

PATENT/Docket No. 4722 EX U.S. Patent 4,486,425 Application for Extension Page 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)

Sankyo Co. Ltd.

Patent Number

4,486,425

Issue Date

4 December 1984

Patent Title

7-[2-(2-Aminothiazol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-

Methoxymethyl-3-Cephem-4-Carboxylates

Commissioner of Patents and Trademarks Box Patent Extension Washington, DC 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 and 37 CFR 1.740

Sir:

Your Applicant, Sankyo Company Limited, represents that it is the Assignee of the entire interest in and to United States Patent No. 4,486,425 granted to Hideo Nakao, Koichi Fujimoto, Sadao Ishihara, Shinichi Sugawara, Isamu Igarashi on the 4th day of December 1984 for 7-[2-(2-Aminothiazol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-Methoxymethyl-3-Cephem-4-Carboxylates. Your Applicant, acting through its duly authorized Agent, The Upjohn Company and the undersigned attorney, hereby submits this application for extension of patent term under 35 USC 156 by submitting the following information required by 37 CFR 1.740. A telefax copy of the Authorization of Agent and Power of Attorney evidencing the appointment of The Upjohn Company and the undersigned as duly appointed Agent is attached hereto as Appendix A. Originals of this document and Appendix F will be forwarded upon their receipt from Japan.

1. <u>Identification of Approved Product</u>

The approved product is cefpodoxime proxetil, the active ingredient in the drugs VANTIN Tablets, VANTIN Oral Suspension, BANAN Tablets, and BANAN Oral Suspension. Cefpodoxime proxetil is a chemical compound otherwise known as $[6R-[6\alpha,7\beta(Z)]]-7-[[(2-A\min o-4-thiazolyl)(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1-[[(1-methylethoxy)carbonyl]oxy]ethyl ester.$

Federal Statute and Applicable Provision Under Which Regulatory Approval Occurred.
 Section 507 of the Federal Food, Drug and Cosmetic Act (21 USC 357; FDC Act)

3. Date Permission Received For Commercial Marketing and Use.

The first received permission for commercial marketing and use of cefpodoxime proxetil under Section 507 of the Federal Food, Drug and Cosmetic Act (21 USC 357) was on 7 August 1992, the date on which the four drugs identified under paragraph (1) above received simultaneous approval.

4. Identification of Active Ingredient in Drug Product and Statement That It has Not Been Previously

Approved For Commercial Marketing or Use Under the Federal Food, Drug and Cosmetic Act,

the Public Health Service Act or the Virus-Serum-Toxic Act.

The sole active ingredient of VANTIN Tablets, VANTIN Oral Suspension, BANAN Tablets and BANAN Oral Suspension is cefpodoxime proxetil. Cefpodoxime proxetil has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. A. Statement That the Application Is Being Submitted Within the 60-Day Period Permitted

For Submission and the Last Day On Which the Application Can Be Submitted.

While this application for patent term extension is not being submitted within sixty (60) days of the date cefpodoxime proxetil received permission for marketing as required under 37 CFR 1.720(f), Applicant nonetheless requests that this application be considered as timely filed since the failure to file within sixty (60) days was unintentional. Thus Applicant requests that the 60 day period referred to in 35 USC 156(d)(1) be interpreted by the Commissioner as commencing on the date that the Applicant first became aware of an unintentional failure to file such application. Attached as Appendix F is a supporting declaration setting forth the circumstances under which the Applicant first became aware of the unintentional failure to file. Since Applicant first became aware of the unintentional error on 4 December 1992, Applicant requests an interpretation that the last day for submission of this application for extension be 2 February 1993.

B. Argument in Support of Submission Date

Public policy supports the remedial interpretation of the duration of the 60 day period as requested by Applicant. Congress has twice in the last decade (PL 97-247 (1982) and PL 102-444 (1992)) amended the patent law to remediate unintentional failures to act. Thus, one can now revive applications which become unintentionally abandoned because of a failure to respond to the PTO or to pay a fee during the period prescribed by statute. (See 35 USC 41(a)(7).) Similarly, 41 USC 41 (c)(1) has recently been amended in the last Congress to permit the payment of maintenance fees up to two years late. While

Unimed V. Quigg, 888 F. 2d 826 (Fed. Cir. 1989) stated that the language in 35 USC 156(d)(1) "on the date the product received permission under the provision of law under which the regulatory review period occurred" meant the FDA approval date, the decision was before the latest statement from Congress evincing a remedial approach to such matters, and involved different facts than those herein. Moreover, the Patent Term Restoration Act is remedial in nature and therefore ought to be broadly construed to achieve Congress' intent. See, also, the reissue statute, 35 U.S.C. 251, which broadly allows for the correction of unintentional errors as well.

As far as the public is concerned, the interpretation Applicant requests will clearly not prejudice anyone, since the extension issue will be resolved well before the patent would otherwise expire, and certainly it would not be as prejudicial as reviving a patent two years after a maintenance fee has not been paid.

For all of the foregoing reasons, Applicant requests this application be treated as timely filed.

6. Identification of Patent For Which Extension Is Being Sought.

Patent No.

4,486,425

Name of Inventors

Hideo Nakao, Koichi Fujimoto, Sadao Ishihara, Shinichi

Sugawara, Isamu Igarashi

Issue Date

4 December 1984

Expiration Date

4 December 2001

7. Copy of Patent

A copy of the patent identified in paragraph 6 hereof is attached as Appendix B.

8. <u>Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments and Re-examination Certificates.</u>

No disclaimers have been made regarding this patent. A certificate of correction has issued on 24 September 1985, and all maintenance fees that were due have been paid. A copy of the Certificate of Correction and the receipts for the maintenance fee payments in this case are attached as Appendix E.

Statement That Patent Claims the Approved Product or Method of Using the approved Product
and Demonstration That Applicable Patent Claims Read on the Approved and Methods of Use.
 U.S. Patent 4,486,425 claims the active ingredient of the approved product, cefpodoxime proxetil.

Claim 1 is the applicable claim.

Claim 1 reads as follows:

A compound of the formula

wherein

R¹ is methyl;

R² is hydrogen or methyl;

and

R³ is a C₁-C₄ alkoxy;

and pharmaceutically acceptable acid addition salts thereof.

The structure of cefpodoxime proxetil is

Cefpodoxime proxetil falls within the scope of this Claim 1 when R² is methyl and R³ is isopropoxy. Claims 3, 4, 5 and 6 also read on cefpodoxime proxetil as they contain these limitations, and Claim 6 is drawn specifically to it. Similarly, cefpodoxime proxetil falls within the scope of corresponding pharmaceutical composition claims 7, 9, 10, 11 and 12, which are correspondingly identical in scope to claims 1, 3, 4, 5 and 6.

10. Relevant Dates During Regulatory Review

Relevant dates and information pursuant to 35 USC 156(g) to enable the Examiner of Health and Human Services to determine the applicable regulatory review period are as follows:

The investigational new drug application, INDA No. 30,254, for cefpodoxime proxetil in tablets, was filed on 2 July 1987. August 2, 1987 was the earliest date upon which clinical trials could begin. The IND for the granules is 33,641.

The new drug application, NDA 50-674, for cefpodoxime proxetil was filed on 30 March 1991.

The new drug application, NDA 50-674, for cefpodoxime proxetil was approved for marketing in the United States on 7 August 1992.

The NDA for VANTIN Oral Suspension is NDA 50-675.

The NDA for BANAN Tablets is 50-687.

The NDA for BANAN Oral Suspension is 50-688.

The NDA filing dates for BANAN Tablets and BANAN Oral Suspension were approximately one week after the VANTIN dates, as Sankyo filed a letter of reference to the corresponding VANTIN files shortly after the NDA's for VANTIN Tablets and VANTIN Oral Suspension were filed.

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11. Brief Description of Activities Undertaken By Applicant During the Applicable Regulatory Period

With Respect to the Approved Product and the Significant Dates Applicable to Such Activities.

A brief description of the activities undertaken by Upjohn and Sankyo Company Limited, Applicant's licensor during the applicable regulatory review period with respect to cefpodoxime and the significant dates applicable to such activities is attached herewith as Appendix C and is a chronology of major communications between Applicant's licensees and the FDA from July 2, 1987, to August 7, 1992, and also includes some communications after that date.

Applicant is authorized by Upjohn to utilize the regulatory review period incurred by Upjohn and the NDA approval granted thereon to Upjohn as the basis of this application for the extension of the patent term of U.S. Patent 4,486,425.

The product names for VANTIN Tablets and VANTIN Oral Suspension were originally DOXEF Tablets and DOXEF Oral Suspension, respectfully, and were changed at the request of the FDA.

12. Applicant's Opinion as to Why the Patent is Eligible for Patent Extension and How the Length of Extension was Determined.

Applicant believes that U.S. Patent No. 4,486,425 is eligible for an extension under 35 USC 156 because it satisfies all of the requirements for such extension including, *inter alia*, the following:

(a) 35 USC 156(a):

U.S. Patent No. 4,486,425 claims a product in the sense that the "product" is a "human drug product" which is defined by the statute [35 USC 156(f)(2) and PTO Rules 37 CFR 7.710(b)(1)] to mean active ingredient of a new drug, i.e., cefpodoxime proxetil;

(b) 35 USC 156(a)(1):

The term of U.S. Patent No. 4,486,425 has not expired prior to submission of the application for extension;

- (c) 35 USC 156(a)(2) and 37 CFR 1.720(b):
 The term of U.S. Patent No. 4,486,425 has never been extended;
- (d) 35 USC 156(a)(3):

This application for extension is submitted by the duly authorized agent of the owner of record of U.S. Patent No. 4,486,425 in accordance with the requirements of 35 USC 156(d) and 37 CFR 1.710;

(e) 35 USC 156(a)(4):

The approved cefpodoxime proxetil containing products were subject to regulatory review prior to their commercial marketing or use;

(f) 35 USC 156(a)(5)(A):

The simultaneous permission for the commercial marketing or use of cefpodoxime proxetil in the four products noted above, after the regulatory review period, is the first permitted commercial marketing or use of cefpodoxime proxetil containing products under the provisions of the FDC Act (21 USC 355) under which such regulatory period matured;

(g) 35 USC 156(c)(4):

No other patent has been extended for the same regulatory review period for products containing cefpodoxime proxetil.

Length of Extension:

Applicant requests an extension of the term of US patent 4,486,425 of 1164 days, or 3.2 years, computed as follows:

- (a) The regulatory review period under 35 USC 156(g)(1)(B) was from August 2, 1987, the date of the IND, to August 7, 1992, the date of NDA approval;
- (b) The period of review under 35 USC 156(g)(1)(B)(i), hereinafter the IND period, was from August 2, 1987 (effective date of IND) until March 30, 1991 (NDA submission date), which is 1336 days or 3.66 years.
- (c) The period of review under 35 USC 156(g)(1)(B)(ii), hereafter the NDA period, was from March 30, 1991 (NDA submission date) until August 7, 1992 (NDA approval date), which is 496 days or 1.35 years.
 - (d) The total regulatory review period under 35 USC 156(g)(1)(B) is 1832 days, or 5.0 years.
- (e) Applicant and Sankyo acted with due diligence during the entire period of regulatory review and therefore the noted term of eligible extension under 35 USC 156(c) should not be shortened for lack of due diligence.
- (f) Under 35 USC 156(c)(2) the period of extension includes only one-half of IND period determined under 35 USC 156(g)(1)(B)(i), i.e., 668 days or 1.83 years.
- (g) In compliance with 35 USC 156(c)(3) the period remaining in the term of U.S. Patent No. 4,486,425 after NDA approval of cefpodoxime proxetil is 9 years 4 months, or 9.3 years. The period of extension, computed as half the IND period, and all of the NDA period, is 1164 days, or 3.2 years, which is less than 5 years as specified in 35 USC 156 (g)(6)(A), and the total of the extension and the period remaining in the term of the patent from the date of marketing approval does not exceed fourteen years, as required under 35 USC 156 (b)(3).

13. Acknowledgment of Duty of Disclosure.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination to be made relative to this application for extension.

14. Fee.

The prescribed fee for receiving and acting upon this application for extension to be charged the Applicant's account as authorized in the accompanying letter which is submitted in duplicate.

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15. The Name, Address and Telephone Number of the Person to Whom Inquires and Correspondence
Relating to the Application for Patent Term Extension are to be Directed:

Lawrence T. Welch Corporate Intellectual Property Law The Upjohn Company 301 Henrietta Street Kalamazoo, MI 49001 Telephone: 616-385-7237

16. Certified Duplicate of Application.

A certified duplicate of this application is attached.

17. Declaration.

The declaration set forth in 37 CFR 1.740(b) for Patent Term Extension under 35 USC 156 is attached as Appendix D.

Respectfully submitted,

Date: 7 Decombon 1992

Lawrence T. Welch, Attorney Registration No. 29,487

Telephone: (616) 385-7237

Mailing Address:

Corp. Intellectual Property Law, The Upjohn Company, Kalamazoo, MI 49001

APPENDIX A

Authorization of Agent and Power of Attorney (Original to be Filed upon Receipt)

PATENT/Docket No. 4722 EX U.S. Patent 4,486,425 Application for Extension Appendix A-1

APPENDIX A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re

U.S. Patent 4,486.425

Issued

4 December 1984

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Hideo Nakuo, Koichi Fujimoto, Sadao Ishihara, Shimichi Sugawara, Isamu

Igarashi

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7-[2-(2-Aminothia:ol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-Methoxymethyl-3-

Cephem-4-Curbosylates

Commissioner of Palents and Trademarks Box Patent Extension Washington, DC 20231

AUTHORIZATION OF AGENT AND POWER OF ATTORNEY

Sir:

Sankyo Co. Ltd., a corporation organized and existing under the laws of Japan and having its head office in Tokyo, Japan, being the owner of record of the above-identified U.S. Letters Patent, hereby authorize and appoint The Upjohn Company, a corporation organized and existing under the laws of Delaware and having its head office at 7000 Portage Road, Kalamazoo, Michigan 49001-0199, and the Attorneys named below:

Robert A. Armitage (Registration No. 27,417) and

Lawrence T. Welch (Registration No. 29,487)

all being employees of The Upjohn Company, individually and collectively to be the agents and attorneys of Sankyo Co. Ltd. with regard to an application for extension of the term of U.S. Parent 4,486,425 under 35 USC 156 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

PATENT/Docket No. 4722 EX U.S. Patent 4.486,425 Application for Extension Appendix A-2

Please address all communication in the above matter to:

Lawrence T. Welch Registration No. 29,487 Corporate Intellectual Property Law The Upjohn Company Kalamazoo, Michigan 49001 (616) 385-7237

SANKYO CO. LTD.

By:

Name:

Title:

Yoshibumi Kawamura

Representative Director

and President

Date: December 4, 1992

APPENDIX B

Copy of U.S. Patent 4,486,425

United States Patent [19]

Nakao et al.

[11] Patent Number:

4,486,425

[45] Date of Patent:

Dec. 4, 1984

[54] 7-[2-(2-AMINOTHIAZOL-4-YL)-2-(SYN)-METHOXYIMINOACETAMIDO]-3-METHOXYMETHYL-3-CEPHEM-4-CAR-BOXYLATES

[75] Inventors: Hideo Nakao; Kolchi Fujimoto; Sadao Ishihara; Shinichi Sugawara; Isamu

Igarashi, all of Hiromachi, Japan

Sankyo Company Limited, Tokyo, Japan

[21] Appl. No.: 304,988

[73] Assignee:

[22] Filed: Sep. 23, 1981

[30] Foreign Application Priority Data

 Sep. 30, 1980 [JP]
 Japan
 55-136449

 Apr. 13, 1981 [JP]
 Japan
 56-55231

 Jun. 10, 1981 [JP]
 Japan
 56-89116

[58] Field of Search 424/246; 544/28

[56] References Cited

U.S. PATENT DOCUMENTS

4,098,888 7/1978	Ochiai et al 544/28
4,278,671 7/1981	Ochiai et a
4,409,215 10/1983	Takaya et al 424/246

FOREIGN PATENT DOCUMENTS

29557 6/1981 European Pat. Off. . 34536 8/1981 European Pat. Off. .

OTHER PUBLICATIONS

"Orally Active Esters of Cephalosporin Antibiotics. II Synthesis and Biological Properties of the Acetoxymethyl Ester of Cefamandole", Walter E. Wright et al., The Journal of Antibiotics, vol. XXXII, No. 11, Nov. 1979, pp. 1155-1160.

"Orally Active Esters of Cephalosporin Antibiotics...", W. J. Wheeler et al., Journal of Medicinal Chemistry, 1979, vol. 22, No. 6, pp. 657-661.

Primary Examiner—Paul M. Coughlan, Jr.
Attorney, Agent, or Firm—Frishauf, Holtz, Goodman & Woodward

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ABSTRACT

Compounds of formula (I):

wherein:

R¹ represents a lower alkyl group selected from methyl group, and ethyl groups;

R² represents a hydrogen atom or a methyl group;

R³ represents a group selected from C₁-C₅ alkoxy groups.

and pharmaceutically acceptable acid addition salts thereof have valuable antibiotic activity and are suitable for oral administration. They may be prepared by a variety of synthetic routes.

12 Claims, No Drawings

7-[2-(2-AMINOTHIAZOL-4-YL)-2-(SYN)-METHOX-YIMINOACETAMIDO]-3-METHOXYMETHYL-3-CEPHEM-4-CARBOXYLATES

The present invention relates to a series of new cephalosporin compounds which are particularly suitable for oral administration, to processes and intermediates for preparing these compounds and to compositions containing the compounds.

Although many cephalosporin derivatives which exhibit excellent antibacterial activity have been discovered, most of them are for parenteral administration. However, except where massive doses of an antibiotic are to be administered quickly, the preferred route of 15 administration is oral, as oral preparations can be administered by the patient himself without the need for trained supervision or assistance. Unfortunately, of the many cephalosporin derivatives discovered, very few possess a combination of superior antibacterial activity, 20 broad antibacterial spectrum against both gram-positive and gram-negative bacteria (especially against Staphylococcus aureus) and the ability to be absorbed efficiently through the digestive tract.

For example, cephalothin, cefazolin and cefmetazole 25 are widely used for parenteral administration, particularly by injection. However, when these compounds are administered orally, only about 5% of the dose administered is recovered in the urine, showing their poor absorption through the digestive tract and their unsuitabil- 30 ity for oral administration. This is thought to be due to the strong dissociation of the carboxy group at the 4position (i.e. the low pKa value) and the strong acidity.

Because of this, many efforts have been made to improve the absorption of cephalosporin derivatives 35 through the digestive tract by esterifying the 4-carboxy group but almost all such efforts have failed to obtain cephalosporin derivatives which are well absorbed through the digestive tract and which are therefore useful for orai administration, as described hereafter, in 40 the one instance where absorption through the digestive tract has been significantly improved, the resulting compound lacks the desired broad antibacterial spectrum.

For example, the Journal of Antibiotics, 32 No. 11, 45 1155 (1979) discloses that the absorption of cefamandol through the digestive tract is not improved by esterification to prepare the acetoxymethyl ester, since this ester is only sparingly soluble in water. Although abimproved to a limited extent by administration of the ester in solution in certain organic solvents (such as propylene glycol), this is not a particularly good solution to the problem.

The Journal of Medicinal Chemistry, 22, 657 (1979), 55 on the other hand, reports that the absorption through the digestive tract of another ester of a cephalosporin which is readily soluble in water, is not significantly improved due to chemical instability of the ester.

Furthermore, it is known that, in general, lower alkyl 60 and benzhydryl esters of cephalosporins possess, in themselves, almost no antibacterial activity and that they are not hydrolyzed in vivo (which might otherwise convert them to an active acid) and hence they are not of value for therapeutic use, although they may be 65 useful as synthetic intermediates.

Of the various cephalosporin derivatives known, one known class has a 2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetamido group at the 7- position and may be represented by the following formula:

(in which B, D and E are substituents).

For example, Japanese Patent Application Kokai (i.e. as laid-open to public inspection) No. 149296/76 which corresponds to U.S. Pat. No. 4,098,888 discloses the following compounds:

- (a) 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxy-
- 3-acetoxymethyl-7-[2-(2-aminothiazol-4-yl)-2-**(b)** methoxyiminoacetamido]-3-cephem-4-carboxylic acid; and
- 7-[2-(2-aminothiazol-4-yl)-2-methox-(c) yiminoacetamido]-3-(1-methyl-1H-tetrazol-5yl)thiomethyl-3-cephem-4-carboxylic acid.

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We have discovered that the percentage recovery of these compounds in urine (which is a measure of their suitability for oral administration is only 3.2%, 1.5% and 2%, for compounds (a), (b) and (c), respectively; these compounds are, accordingly, unsuitable for oral administration.

Likewise, Jamese Patent Application Kokai No. 86188/81 published July 13, 1981 which corresponds to European Patent Application No. 29,557 published June 3, 1981 (both published after the Sept. 30, 1980 filing date of the priority Japanese Application No. 136449/1980) disclose. 7-[2-(2-aminothiazol-4-yl)-2methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid (d), which is the free carboxylic acid corresponding to certain of the compounds of the present invention. We have, however, found that the recovery rate in urine of compound (d) is only 5.5% and it is, therefore, unsuitable for oral administration. The Specification also discloses certain esters, particularly the t-butyl and benzhydryl esters, of cephalosporin compounds related to compound (d). However, as stated above, such esters are not believed to be readily convertible in vivo to the corresponding carboxylic acid and, as a result, may not be effective in actual use.

Japanese Patent Application Kokai No. 9296/79 sorption of the ester through the digestive tract can be 50 which corresponds to U.S. Pat. No. 4,278,793 and 34795/78 which corresponds to U.S. Pat. No. 4,278,671 disclose the following pivaloyloxymethyl esters:

- 3-acetoxymethyl-7-[2-(2pivaloyloxymethyl aminothiazol-4-yl)-2-methoxyiminoacetamido]-3cephem-4-carboxylate and
- (f) pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2methoxyiminoacetamido]-3-(1-methyl-1H-tetrazol-5-yl)-thiomethyl-3-cephem-4-carboxylate.

We have also found that the recovery rate in urine of these compounds is only 8% and 14% for compounds (e) and (f), respectively, and these compounds also are unsuitable for oral administration.

Comparing the recovery rates of compounds (a), (b) and (c) with the recovery rates of compounds (e) and (f), the results are rather surprising, since it is known that the absorption of ampicillin through the digestive tract is considerably improved by converting it to the pivaloyloxymethyl ester.

The above-mentioned Japanese Patent Application Kokai No. 34795/78 also discloses pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylate, hereinafter referred to as "compound (g)". We have carried out extensive studies of this compound and have found that it exhibits very good recovery in urine, at a level almost comparable with that of the compounds of the present invention, thus suggesting that it may well be suitable for oral administration. However, as will be shown hereafter, 10 compound (g), when administered orally, is hydrolyzed and converted in vivo to the corresponding carboxylic acid which, in turn, has poor activity against Staphylococcus aureus. Failure to inhibit the growth of this bacterium, which is perhaps one of the most important from 15 the clinical point of view, could be a disadvantage in actual use.

It is, accordingly, clear from the above discussion that preparation of a cephalosporin derivative which meets the triple requirements of good absorption 20 through the digestive tract, high antibacterial activity and a broad antibacterial spectrum, is not a simple matter. The cephalosporin nucleus includes many points at which different substituents may be introduced and the introduction of a particular substituent to improve one 25. property may adversely affect other properties in a quite unpredictable way. Moreover, it has clearly been demonstrated that, even where a particular chemical modification is known to improve the properties of one particular compound (e.g. as with the preparation of the 30 pivaloyloxymethyl ester to improve the absorption of ampicillin), this is not any indication that a ..milar modification will similarly improve the properties of any other compound.

We have now surprisingly discovered a limited class 35 of cephalosporin derivatives which can be administered orally as they are readily absorbed through the digestive tract and which are then readily hydrolyzed and converted in vivo to the corresponding carboxylic acid which, in turn, shows quite outstanding activity against 40 both gram-positive and gram-negative bacteria.

Accordingly, the present invention consists in compounds of formula (I):

in which:

R1 represents a methyl group or an ethyl group, R² represents a hydrogen atom or a methyl group;

and

R3 represents a C1-C3 alkyl or alkoxy group; and pharmaceutically acceptable acid addition salts

The invention also provides a pharmaceutical composition comprising, as active ingredient, one or more of the compounds of the invention in admixture with a pharmaceutically acceptable carrier or diluent.

The invention also provides a variety of processes for 65 preparing the compounds of the invention.

In the compounds of formula (I), when R³ represents an alkyl group having from 1 to 5 carbon atoms, it is

preferably a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl or t-pentyl group, most preferably a t-butyl group. R3 most preferably represents an alkyl group having from 1 to 5 carbon atoms when R2 represents a hydrogen atom.

When R³ represents an alkoxy group having from 1 to 5 carbon atoms, it is preferably a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy or 1-ethylpropoxy group, most preferably an ethoxy group. R3 most preferably represents an alkoxy group having from 1 to 5 carbon atoms when R² represents a methyl group.

Examples of compounds of the invention are given in the following list; the compounds are hereafter identified by the numbers assigned to them in the list.

Acetoxymethyl 7-[2-(2-aminothiazol-4-yl)-2methoxyiminoacetamido]-3-methoxymethyl-3cephem-4-carboxylate

2. Propionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2methoxyiminoacetamido]-3-methoxymethyl-3cephem-4-carboxylate

1-Acetoxyethyl 7-[2-(2-aminothiazol-4-yl)-2methoxyiminoacetamido]-3-methoxymethyl-3cephem-4-carboxylate

4. Propionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

5. Isopropionyloxymethyl 7-[2-(2-aminothiazol-4-yl)-cephem-4-carboxylate

Butyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

7. 1-Propionyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2ethoxyiminoscutamido]-3-methoxymethyl-3-cephem-4-carboxylate

8. Isobutyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2methoxyiminoacetamido]-3-methoxymethyl-3cephem-4-carboxylate

9. Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2methoxyiminoacetamido]-3-methoxymethyl-3cephem-4-carboxylate

10. Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

11. Isovaleryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2methoxyiminoacetamido]-3-methoxymethyl-3cephem-4-carboxylate

12. 1-Pivaloyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

Methoxycarbonyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate

1-Methoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

15. Ethoxycarbonyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

16. 1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

17. 1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

18. Propoxycarbonyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

19. 1-Isopropoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate

20. 1-Butoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

Isobutoxycarbonyloxymethyl 7-[2-(2-amino-10 thiazol-4-yl)-2-methoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate

1-sec-Butoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate

7-[2-(2-1-(1-Ethylpropoxycarbonyloxy)ethyl aminothiazol-4-yl)-2-methoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate

24. 1-(1-Ethylpropoxycarbonyloxy)ethyl 7-[2-(2aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate

3,3,3-Trimethylpropionyloxymethyl aminothiazol-4-yl)-2-methoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate.

Of the compounds listed above, Compounds No. 9, 25 10, 16 and 17 are most preferred.

As indicated in the formula, the compounds of formula (I) of the present invention are in the synform which has been found to have much stronger antibacterial activity than the corresponding anti-isomers.

The compounds of formula (I) will form acid addition salts with various acids and the invention thus also includes such salts with pharmaceutically acceptable acids, for example inorganic acids (such as hydrochloric acid, sulphuric acid or phosphoric acid) or organic 35 acids (such as methanesulphonic acid, benzenesulphonic acid or malonic acid). Of the acid addition salts, the hydrochlorides are most preferred.

The compounds of the present invention may be prepared by a number of methods, for example those 40 described below.

Method 1

ing a compound of formula (II):

(in which R4 represents an amino group or a protected amino group, and R1 is as defined above) or a reactive 55 derivative of said compound of formula (II) with a compound of formula (III):

(in which R² and R³ are as defined above) and, if necessary, deprotecting the group R4.

In the above compounds of formula (II), preferred amino-protecting groups included in R4 are those groups which may readily be removed to restore a free amino group, for example the trityl, formyl, t-butoxyearbonyl or 2-ethoxycarbonyl-1-methylvinyl groups, which may be removed by treatment with an acid, the 2.2.2-trichloroethoxycarbonyl group, which may be removed by reduction, the 2-methanesulphonylethoxyearbonyl group, which may be removed by treatment with an alkali, or the chloroacetyl group, which may be removed by treatment with thiourea.

The carboxylic acid of formula (II) may itself be used 15 in the free form or it may be used in the form of a reactive derivative. Suitable reactive derivatives include the acid halide, the acid anhydride, mixed acid anhydrides, reactive esters, reactive amides and the acid azide. Preferred mixed acid anhydrides include mixed acid anhydrides with mono-(lower alkyl)carbonates, such as monomethyl carbonate or monoisobutyl carbonate, and mixed acid anhydrides with lower alkanoic acids, such as pivalic acid or trichloroacetic acid. Preferred reactive esters include the p-nitrophenyl ester, the pentachlorophenyl ester and the N-hydroxyphthalimide es-

Where the compound of formula (II) is employed in the form of the free acid, we prefer to carry out the reaction in the presence of a condensing agent. Examples of suitable condensing agents include: di-substituted carbouilmides, such as dicyclohexylcarbodiimide, imidazolides, such as carbonyldiimidazole or thionyldiimidazole; N-ethoxycarbonyl-2-ethoxy-1,2dihydroquinoline, or a Vilsmeier reagent prepared from dimethylformamide and, for example, phosphorus oxychloride or thionyl chloride.

Where a reactive derivative of the acid (II) is employed, the use of such a condensing agent is not necessary; however, for certain reactive derivatives, it may be desirable to carry out the reaction in the presence of a base. Examples of suitable bases include: alkali metal compounds, such as sodium bicarbonate, potassium bicarbonate, sodium carbonate or potassium carbonate; or aliphatic, aromatic or nitrogen-containing heterocy-Compounds of formula (I) can be prepared by react- 45 clic bases, such as triethylamine, N,N-dimethylamiline, N,N-diethylaniline, N-methylpiperidine, N-methylpyrrolidine, pyridine, collidine or lutidine.

The reaction of the acid (II) or its reactive derivative with the compound of formula (III) is preferably ef-50 fected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Preferred solvents include inert organic solvents (such as acetone, methyl ethyl ketone, tetrahydrofuran, dioxan, ethyl acetate, chloroform, methylene chloride, acetonitrile, dimethylformamide or dimethylsulphoxide) or a mixture of such a solvent and

There is no particular limitation on the reaction temperature, but we normally prefer to conduct the reac-(III) 60 tion at ambient temperature or with cooling. The time required for the reaction will vary, depending mainly upon the method of acylation and the reaction temperature, but usually the reaction will require a period which may vary from several tens of minutes to several 65 tens of hours.

After completion of the reaction, the reaction product may be recovered from the reaction mixture by conventional means. For example, if a water-miscible sary, be further purified by conventional means, for 10

example by chromatographic techniques.

The reaction required to remove the protecting group, if R⁴ represents a protected imino group, is, as mentioned above, conventional and will vary depending upon the particular protecting group chosen. After 15 removal of the protecting group, the desired product may be recovered from the reaction mixture and purified, e.g. as suggested above, to give the desired compound of formula (I).

Method 2

Compounds of formula (I) may be obtained by reacting a compound of formula (IV):

(in which R¹ and R⁴ are as defined above) or a reactive derivative thereof with a compound of formula (V):

(in which X represents a halogen atom, such as a chlorine, bromine or iodine atom, preferably an iodine atom, and R² and R³ are as defined above) and then, if necessary, deprotecting the group represented by R⁴.

Preferred reactive derivatives of the compound of formula (IV) are salts, for example salts with a metal 45 (such as sodium or potassium) or with an organic amine (such as triethylamine). Where the free acid (IV) is employed, the reaction is preferably effected in the presence of an acid-binding agent, which may be organic or inorganic, for example potassium carbonate, sodium carbonate, sodium bicarbonate, triethylamine, dicyclohexylamine, pyridine or N,N-dimethylaniline.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable 55 solvents include dimethylformamide, dimethylacetamide, dimethyl sulphoxide, hexamethylphosphoric triamide or acetonitrile, a mixture of two or more such solvent may be employed, as may a mixture of one or more of these solvents with one or more other inert organic 60 solvents. The reaction may be effected over a wide range of temperatures, but we generally prefer to conduct it at ambient temperature or with cooling. The time required for the reaction may vary from a period of several minutes to several hours.

After completion of the reaction, the reaction mixture is preferably diluted with a water-immiscible solvent, washed successively with an aqueous solution of potassium bisulphate and an aqueous basic solution and then dried, after which the solvent is distilled off to give the desired product. This product may be further purified by conventional means, for example by chromatographic techniques.

Where R⁴ represents a protected amino group, it may be converted to a free amino group as described in Method 1.

Method 3

Compounds of formula (I) may be obtained by reacting a compound of formula (VI):

(in which R^5 represents an alkyl group or an aryl group, and R^1 , R^2 and R^3 are as defined above) with thioures. Compounds of formula (VI) are new and themselves form part of the present invention.

In the compounds of formula (VI), when R⁵ represents an alkyl group, it is preferably an alkyl group having from 1 to 6 car ... atoins, for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl group, more preferably a methyl or ethyl group. When R5 represents an aryl group, it is preferably a substituted or unsubstituted phenyl or naphthyl group. In the case of substituted groups, there may be one or more substituents, normally from 1 to 5 substituents, and they may be the same or different. Suitable substituents include C1-C4 alkyl groups (e.g. methyl, ethyl, propyl, isopropyl or butyl), C1-C4 alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy or isobutoxy) and halogen atoms (e.g. chlorine, bromine or fluorine atoms). The most preferred aryl groups represented by R⁵ are the phenyl and p-methylphenyl groups.

Representative examples of compounds of formula (VI) include:

 Acetoxymethyl 7-(2-methoxyimino-3-oxo-4-ptoluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 1-Acetoxyethyl 7-(2-ethoxyimino-3-oxo-4-ptoluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 Propionyloxymethyl 7-(4-benzenesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 1-Propionyloxyethyl 7-(4-methanesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 1-Butyryloxyethyl 7-(4-ethanesulphonyloxy-2ethoxyimino-3-oxobutyrylamino)-3-methoxymethyi-3-cephem-4-carboxylate

31. Isobutyryloxymethyl 7-(2-methoxyimino-3-oxo-4p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

32. Pivaloyloxymethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 Pivaloyloxymethyl 7-(2-ethoxyimino-3-oxo-4-ptoluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

34. Pivaloyloxymethyl 7-(4-benzenesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methox-ymethyl-3-cephem-4-carboxylate

Pivaloyloxymethyl 7-(4-methanesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

Pivaloyloxymethyl 7-(4-ethanesulphonyloxy-2-10 ethoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 1-Pivaloyloxyethyl 7-(2-methoxyimino-3-oxo-4-ptoluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

38. Methoxycarbonyloxymethyl 7-(4-methanesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 Ethoxycarbonyloxymethyl 7-(4-benzenesulphonyloxy-2-ethoxyimino-3-oxobutyrylamino)-3methoxymethyl-3-cephem-4-carboxylate

 1-Ethoxycarbonyloxyethyl 7-(2-methoxyimino-3oxo-4-p-toluenesulphonyloxybutyrylamino)-3methoxymethyl-3-cephem-4-carboxylate

41. 1-Ethoxycarbonyloxyethyl 7-(4-methanesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 1-Ethoxycarbonyloxyethyl 7-(2-ethoxyimino-3oxo-4-p-toluenesulphonyloxybutyrylamino)-3methoxymethyl-3-cephem-4-carboxylate

 Isopropoxycarbonyloxymethyl 7-(2-methoxyimino-3-oxo-4-p-toluc.. sulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4carboxylate.

44. 1-Butoxycarbonyloxyethyl 7-(4-benzenesulphonyloxy-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

45. 1-(1-Ethylpropoxycarbonyloxy)ethyl 7-(2methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4carboxylate

46. 3,3,3-Trimethylpropionyloxymethyl 7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4carboxylate

Compounds of formula (VI) may be prepared, for example, by reacting a compound of formula (VII):

(in which R¹ and R⁵ are as defined above) or a reactive derivative thereof with a compound of formula (III):

(in which R² and R³ are as defined above). Compounds of formula (VII) are new and also part of the present invention. Representative examples of compounds of formula (VII) include:

47. 2-Methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyric acid

48. 2-Ethoxyimino-3-oxo-4-p-toluenesulphonyloxybutyric acid

 49. 4-Benzenesulphonyloxy-2-methoxyimino-3-oxobutyric acid

 4-Methanesulphonyloxy-2-methoxyimino-3-oxobutyric acid

 4-Ethanesulphonyloxy-2-ethoxyimino-3-oxobutyric acid.

Compounds of formula (VII) may, for example, be prepared by the series of reactions illustrated in the following reaction scheme for the preparation of the compound in which R⁵ represents a p-tolyl group and R³ represents a methyl group:

BrCH₂COC(CH₃)₃ + T₅OA₈
$$\longrightarrow$$

T₅OCH₂COC(CH₃)₃ $\xrightarrow{NaNO_2}$

T₅OCH₂COCCOOC(CH₃)₃ $\xrightarrow{(CH_3)_2SO_4}$

OH

T₅OCH₂COCCOOC(CH₃)₃ $\xrightarrow{H^{\oplus}}$

OCH₃

T₅OCH₂COCCOOC(CH₃)

OCH₃

T₅OCH₂COCCOOCH

In the reaction to prepare the compound of formula (VI), the free acid or formula (VII) may be used as such or a reactive derivative of this free acid may be used.

(VII) 50 Where the free acid is used, the reaction is preferably carried out in the presence of a condensing agent, for example: a disubstituted carbodiimide, such as N,N'-dicyclohexylcarbodiimide; an azolide compound, such as N,N'-carbonylimidazole, a dehydrating agent, such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride or an alkoxyacetylene; or a Vilsmeier reagent prepared from dimethylformamide and phosphorus oxychloride.

Where a reactive derivative of the acid of formula (VII) is employed, no such condensing agent is needed, but, depending upon the nature of the reactive derivative, the reaction may preferably be carried out in the presence of a base. Suitable bases include, for example: alkali metal compounds, such as sodium bicarbonate, 50 potassium bicarbonate, sodium carbonate or potassium carbonate; and aliphatic, aromatic or nitrogen-containing heterocyclic bases, such as triethylamine, N,N-diethylaniline, N-methylpiperi-

Preferred reactive derivatives of the acid (VII) include the acid halide, the acid anhydride, mixed acid anhydrides, active esters, active amides and the acid 5 azide. Suitable mixed acid anhydrides include those with monoesters of carbonic acid (for example monomethyl carbonate or monoisobutyl carbonate) and those with lower alkanoic acids or lower halcalkanoic acids (such as pivalic acid or trichloroacetic acid). Suitable 10 active esters include, for example, the p-nitrophenyl ester, the pentachlorophenyl ester, the N-hydroxyphthalimide ester and the N-hydroxybenzotriazole ester.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided 15 that it has no adverse effect upon the reaction. Suitable solvents include acetone, tetrahydrofuran, dioxan, ethyl acetate, chloroform, methylene chloride, dimethylformamide, acetonitrile and water, as well as mixtures of two or more of these solvents.

The reaction temperature is not particularly critical and the reaction is therefore normally performed at room temperature or with cooling. The time required for the reaction will vary, depending mainly on the nature of the acylating agent and on the reaction temperature, but the reaction will normally be complete within from 10 minutes to several tens of hours.

Upon completion of the reaction, the desired compound of formula (VI) may be recovered from the reaction mixture by conventional means and, although the 30 compound may, if necessary, be purified (for example by recrystallization or by the various chromatographic techniques) it may also be used, without untermediate purification or separation, for the next step, that is to say the preparation of the desired compound of formula (I).

The reaction to produce the compound of formula (I) comprises contacting the compound of formula (VI) with thiourea, preferably in the presence of a suitable solvent. The nature of the solvent is not critical, provided that it has no adverse effect upon the reaction. 40 Suitable solvents include water, methanol, ethanol, dimethylformamide, dimethylacetamide, acetonitrile, tetrahydrofuran and mixtures of two or more of these solvents.

If desired, a base (such as sodium acetate or sodium 45 bicarbonate) may be added to the reaction mixture in order to promote the reaction or assist it to go to completion. Formation of by-products may be prevented by effecting the reaction in the presence of a buffer solution of pH 6.5-7.

The amount of thiourea employed is preferably 1 or more equivalents per equivalent of said compound of formula (VI).

The reaction temperature is not particularly critical and the reaction is therefore preferably effected at ambient temperature. The time required for the reaction will vary, depending upon the reaction conditions, but a period of from several tens of minutes to several hours will generally be required.

Upon completion of the reaction, the desired compound of formula (I) may be recovered by conventional means, for example by concentration under reduced pressure, extraction, reprecipitation or chromatography.

Method 4

65

Compounds of formula (I) may also be obtained by reacting a compound of formula (VIII):

12

(in which R^1 , R^2 and R^3 are as defined above) with thioures.

Compounds of formula (VIII), which are new and also form part of the present invention, may be prepared by nitroscating a compound of formula (IX):

(in which \mathbb{R}^2 and \mathbb{R}^3 are as defined above) to give a compound of formula (X):

(in which R² and R³ are as defined above) and then alkylating the hydroxy group attached to the imino nitrogen atom of said compound of formula (X).

Representative examples of the new compounds of formula (VIII) include:

- Acetoxymethyl 7-(4-chloro-2-methoxymino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
- 1-Acetoxyethyl 7-(4-chloro-2-methoxyimino-3oxobutyrylamino)-3-methoxymethyl-3-cephem-4carboxylate
- 1-Propionyloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3cephem-4-carboxylate
- 1-Ethoxycarbonyloxyethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3cephem-4-carboxylate
- 1-Ethoxycarbonyloxyethyl 7-(4-chloro-2-ethoxymino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
- Methoxycarbonyloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methox-ymethyl-3-cephem-4-carboxylate
- Ethoxycarbonyloxymethyl 7-(4-chloro-2-ethoxymino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate
- Isopropoxycarbonyloxymethyl 7-(4-chloro-2methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

yimino-3-oxobutyrylamino)-3-methoxymethyl-3cephem-4-carboxylate

 1-Propionyloxyethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3cephem-4-carboxylate

 i-Butyryloxyethyl 7-(4-chloro-2-ethoxyimino-3oxobutyrylamino)-3-methoxymethyl-3-cephem-4carboxylate

63. Isovaleryloxymethyl 7-(4-chloro-2-methox- 10 yimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

64. Pivaloyloxymethyl 7-(4-chloro-2-methoxymino-3-oxobutyrylanino)-3-methoxymethyl-3-cephem-4-carboxylate

Pivaloyloxymethyl 7-(4-chloro-2-ethoxymino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 Isobutyryloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3cephem-4-carboxylate

67. 1-Pivaloyloxyethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

68. 1-(1-Ethylpropoxycarbonyloxy)ethyl 7-(4-chloro-25 2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

 3,3,3-Trimethylpropionyloxymethyl 7-(4-chloro-2-methoxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate.

The compound of formula (IX) can be prepared by acylating a compound of formula (III):

(in which R2 and R3 are as defined above) with 4 chloro-3-oxobutyryl chloride (which can be obtained by reacting diketene with chlorine). This acylation may 45 be conducted by conventional means and is preferably effected in a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include methylene chloride, chloroform, tetrahydrofuran and dioxan. The acylation is 50 preferably conducted in the presence of a base, preferably an organic base such as triethylamine, pyridine, N,N-dimethylaniline or N,N-diethylaniline. The reaction is preferably effected at about ambient temperature or at a lower temperature and will normally require a 55 period of from several minutes to several hours. After completion of the reaction, the product of formula (IX) may be recovered and purified by conventional means, for example concentration, extraction with organic solvents, chromatographic techniques or recrystalliza- 60

The nitrosoation of the compound of formula (IX) to prepare the compound of formula (X) may be effected by techniques known for the nitrosoation of reactive methylene groups. Such a nitrosoation reaction is normally effected using a metal salt of nitrous acid under acidic conditions or an ester of nitrous acid under suitable conditions. However, when preparing the com-

pounds of the invention, it is necessary to carry out the reaction under such conditions that the cephalosporin ring system and the chlorine atom on the side chain at the 7-position do not participate in the reaction. It is, accordingly, desirable to carry out the reaction under weakly acidic or weakly basic conditions at a temperature below ambient. This reaction is normally carried out in the presence of a solvent, the nature of which is not critical, provided that it is capable of dissolving the compound of formula (IX) and does not have any adverse effect upon the reaction. Suitable solvents include formic acid, acetic acid, tetrahydrofuran, methanol, ethanol, chloroform, ethyl acetate and benzene, or a mixture of water with one or more of these solvents. The particular solvent chosen will depend upon the nature of the nitrosoating agent.

Examples of metal salts of nitrous acid employed as the nitrosoating agent include alkaline metal salts (such as sodium nitrite or potassium nitrite), preferably sodium nitrite. The nitrous acid ester is preferably an ester with a lower alcohol, for example pentyl nitrite or butyl nitrite.

Where a metal salt of nitrous acid is used as the nitrosoating agent, the reaction must be carried out under acidic conditions and, if an acidic solvent (such as formic acid or acetic acid) is not employed, the addition of an acid (which may be organic or inorganic) is necessary. Accordingly, we prefer to carry out the reaction using formic acid or acetic acid as the reaction solvent.

The reaction is .efe: ably carried out at about ambient temperature or below and will require a period which may range from several minutes to several hours.

After completion of the reaction, the resulting prod-35 uct of formula (X) may be isolated and purified by conventional means, for example by concentration, extraction with organic solvents or chromatographic techniques.

The alkylation of the resulting compound of formula (X) to give the compound of formula (VIII) may be effected by reacting the compound of formula (X) with an alkylating agent, preferably in the presence of a solvent. The nature of the solvent is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include acetone, tetrahydrofuran, dioxan, methanol, ethanol, chloroform, ethyl acetate, diethyl ether and dimethylformamide, or a mixture of two or more of these solvents.

Suitable alkylating agents include dialkyl sulphates (e.g. dimethyl sulphate or diethyl sulphate), diazoal-kanes (e.g. diazomethane) and alkyl halides (e.g. methyl iodide or ethyl iodide).

Except when a diazoalkane (such as diazomethane) is used as the alkylating agent, the reaction is preferably effected in the presence of a base. Suitable bases include: alkali metal carbonates, such as sodium carbonate or potassium carbonate; alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide; and nitrogen-containing organic bases, such as triethylamine, pyridine or N,N-dimethylaniline.

The reaction is preferably effected at ambient temperature or below and will normally require a period of from several minutes to several hours. After completion of the reaction, the desired compound of formula (VIII) may be isolated and purified by conventional means, for example concentration, extraction with organic solvents, chromatographic techniques or recrystallization.

The reaction of the compound of formula (VIII) with thiourea to give the desired compound of formula (I) is essentially the synthesis of an aminothiazole derivative by reacting a haloketone with thiourea and may be carried out in much the same way as is common for this 5 type of reaction.

The reaction is usually carried out in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. The solvent is preferably an organic solvent (such as dimethylformamide, dimethylacetamide, methanol, ethanol or tetrahydrofuran) or a mixture of water with one or more of these organic solvents.

The thiourea is preferably employed in an amount of 1 or more equivalents per equivalent of said compound of formula (VIII).

In order to accelerate the reaction, sodium iodide may be added to the reaction mixture and the hydrogen chloride formed in the reaction may be neutralized by the addition of a neutral phosphate buffer solution.

The reaction is preferably effected at ambient temperature and will normally be complete within a period of from 1 to 10 hours.

When the reaction is complete, the desired compound of formula (I) may be isolated and purified by conventional means, for example by concentration, extraction with organic solvents, chromatographic techniques, reprecipitation or recrystallization.

Compounds of formula (I) may also be obtained by reacting a compound of formula (XI):

(in which R², R³ and R⁴ are as defined above) with a compound of formula (XIII):

 H_2N —O—R¹ (XII) (in which R¹ is as defined above) and then, if necessary, deprotecting the group represented by R⁴.

Compounds of formula (XI) are new and also form 50 part of the present invention. They may be prepared by reacting a compound of formula (XIII):

(in which R⁴ is as defined above) or a reactive derivative thereof with a compound of formula (III).

Representative examples of the novel compounds of formula (XI) include:

 Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3-cephem-4-carboxylate

 Pivaloyloxymethyl 7-[2-(2-formamidothiazol-4yl)glyoxylamido}-3-methoxymethyl-3-cephem-4carboxylate 72. 1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3-cephem-4carboxylate

 1-Ethoxycarbonyloxyethyl 7-[2-(2-formamidothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3cephem-4-carboxylate.

In the reaction to produce the compound of formula (XI), the compound of formula (XIII) may be used either in the form of the free acid or in the form of a reactive derivative thereof. When the free acid is used, the reaction is preferably effected in the presence of a condensing agent, for example: a disubstituted carbodimide, such as N,N'-dicyclohexylcarbodiimide, an imidazolide, such as N,N'-carbonylamidazole or thionyldiimidazole, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; or a Vilsmeier reagent prepared from dimethylformamide and phosphorus oxychloride or thionyl chloride.

On the other hand, where a reactive derivative of the acid (XIII) is employed, there is no need to use a condensing agent, but, depending upon the nature of the reactive derivative, it may be preferred to effect the reaction in the presence of a base. Suitable bases include: alkali metal compounds, such as sodium bicarbonate, potassium bicarbonate, sodium carbonate or potassium carbonate; and aliphatic, aromatic or nitrogen-containing heterocyclic bases, such as triethylamine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, pyridine, collidine or lutidine.

30 Reactive derivatives of the acid (XIII) include the acid halides, the acid anhydride, mixed acid anhydrides, active esters, active amides and the acid azide. Examples of suitable mixed acid anhydrides include those with monoesters of carbonic acid (for example monomethyl carbonate or monoisobutyl carbonate) and those with lower alkanoic acids and lower haloalkanoic acids (such as pivalic acid or trichloroacetic acid). Suitable active esters include, for example, the p-nitrophenyl ester, the pentachlorophenyl ester, the N-hydroxyph-40 thalimide ester and the N-hydroxybenzotriazole ester.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include acetone, methyl ethyl ketone, tetrahydrofuran, dioxan, ethyl acetate, chloroform, methylene chloride, dimethylformamide, acetonitrile and dimethyl sulphoxide, and mixtures of these solvents with water.

There is no particular limitation on the reaction temperature and accordingly the reaction is preferably effected at ambient temperature or with cooling. The time required for the reaction will vary, depending mainly on the nature of the acylating method and on the reaction temperature, but it will normally require a period of from 10 minutes to several tens of hours.

After completion of the reaction, the compound of formula (XI) may be recovered from the reaction mixture by conventional means and it may, if desired then be purified by conventional techniques such as chromatography.

The reaction of the compounds of formulae (XI) and (XII) is normally performed in a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include dimethylformamide, dimethylacetamide, acetonitrile and various alcohols, as well as mixtures of these solvents with water.

The alkoxyamine of formula (XII) is preferably employed in the form of a salt with an inorganic acid (such

as hydrochloric acid, nitric acid or sulphuric acid) or an organic acid (such as acetic acid or benzoic acid).

The reaction temperature is not critical, but we normally prefer to carry out the reaction at a temperature from ambient temperature to 60° C. The time required 5 for the reaction may vary, depending upon the reaction conditions, but will generally be from 10 minutes to several hours.

After completion of the reaction, the desired compound of formula (I) may be recovered from the reaction mixture by conventional means, for example by adding water and a water-immiscible solvent (such as ethyl acetate) to the reaction mixture, separating the organic layer under slightly alkaline conditions from the aqueous layer and then removing the organic solvent by distillation from this organic layer to give the desired compound.

Where the group R⁴ in the compound obtained by this process is a protected amino group, it may be deprotected using the techniques described in relation to 20 Method 1.

The desired compound of formula (I) may, if necessary, be purified by conventional means such as recrystallization and/or chromatographic techniques.

The compounds of formula (1) and their acid addition salts may advantageously be employed in antibacterial compositions for oral administration. In order that a compound may be used for this purpose, it is essential, as mentioned above, that it should be well absorbed through the digestive tract after oral administration. Good absorption through the digestive tract is demonstrated by a good recovery of the compound or of degration products in the urine after oral administration.

The prior art compound (g) has a recovery rate in urine of 66.7%, which is very nearly comparable with the recovery rates of 75.9% and 78% of Compounds 5 and 6, which are representative of the compounds of the present invention. These figures are quite satisfactory for the purposes of oral administration.

However, in addition to this good absorption through the digestive tract, it is desirable that compounds such as the prior art compound (g) and the compounds of the invention should, after hydrolization in vivo, be very active against gram-positive and gram-negative bacteria. The compounds of the invention, as well as compound (g), are hydrolized in vivo to the corresponding carboxylic acids and hence it is the antibacterial activities of these carboxylic acids, rather than of the esters, which are important from the clinical point of view. The activities of the carboxylic acids corresponding to Compounds No. 5 and 6 and to compound (g) against various bacteria are shown in the following Table, in terms of their minimal inhibitory concentrations (µg/ml).

TABLE

		<u> </u>	
	Compound 5	Compound 6	Compound (g)
Staphylococcus aureus 209P	0.4	0.2	12.5
Staphylococcus aureus 56	0.8	0.4	25
Escherichia coli N1HJ	0.4	0.8	0.8
Escherichia coli 609	0.4	0.8	0.8
Shigella flexneri 2a	0.8	0.4	0.8
Klebsiella pneumoniae	0.1	0.2	0.2

TABLE-continued

	Compound 5	Compound 6	Compound (g)
Klebsiella sp. 846	0.8	0.8	1.5
Proteus vulgaris	0.01	0.01	<0.1
Salmonella enteriti- dis G.	0.2	0.4	0.4

It is clear from the above Table, that the compounds of the invention and the prior art compound are all highly active against gram-negative bacteria, when administered orally. However, whereas Compounds 5 and 6 are active against Staphylococcus aureus, which is representative of the gram-positive bacteria, compound (g) has a rather low activity against these bacteria.

The compounds of the invention are preferably administered orally, for example in the form of capsules, tablets, powders, syrups or suspensions. The dosage depends upon the age, symptoms and body weight of the patient and on the duration of treatment, but the dosage may normally range from 0.2 g to 5 g per day, preferably from 0.5 g to 3 g per day for adults; however, if necessary, larger doses may be employed.

In the pharmaceutical compositions of the present invention, any conventional pharmaceutically acceptable carrier or diluent may be employed in admixture with the active compound or compounds. As the composition is generally intended to be administered orally, it is desirably presented in a form readily absorbed through the stomach or intestines. Tablets or capsules are normally in unit dosage form and may contain binding agents (e.g. syrup, gum crabic, gelatin, sorbitol, gum tragacanth or polyvinylpyrrolicione), diluents (e.g. lactose, sugar, corn starch, calcium phosphate, sorbitol or glycine), lubricants, (e.g. magnesium stearate, talc, polyethylene glycol or silica), disintegrating agents (e.g. potato starch) or wetting agents (e.g. sodium lauryl sulphate) or any combination thereof. The tablets may, if desired, be coated, e.g. with an enteric coating, as is well-known in the art.

Liquid formulations may be aqueous or oily suspensions, syrups, elixirs or similar compositions. Alternatively, the composition may be a dried product which can then be redissolved in water or another suitable vehicle before administration. Such liquid formulations may contain conventional additives, such as suspending agents (e.g. sorbitol syrup, methylcellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fat), emulsifying agents (e.g. lecithin, monocleic acid sorbitol or gum arabic), nonaqueous vehicles (e.g. almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol) or any combination of two or more thereof.

When the composition of the invention is formulated in unit dosage form, it preferably contains from 50 to 500 mg of the compound or compounds of the invention per unit dose.

The preparation of the compounds of the present invention is further illustrated by the following Examples and the preparation of certain intermediates is illustrated by the following Preparations. The compounds of the invention are all in the syn configuration.

PREPARATION I

Pivaloyloxymethyl 3-methoxymethyl-7-phenoxyacetamido-3-cephem-4carboxylate

of sodium 3-methoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate was disssolved in 50 ml of dimethyl sulphoxide, and 975 mg of pivaloyloxymethyl bromide were added thereto, after which the mixture was stirred at room temperature for 15 minutes. The mixture was then diluted with 200 ml of ethyl acetate, washed in turn with 50 ml of a saturated aqueous solution of sodium bicarbonate and 50 ml of a saturated squeous solution of potassium bisulphate, and then 15 dried over anhydrous magnesium sulphate. After filtering off the drying agent, the filtrate was concentrated under reduced pressure and the resulting residue was chromatographed through 100 g of silica gel eluted with a 1:1 by volume mixture of hexane and ethyl ace- 20 tate, to afford 750 mg of the desired pivaloyloxymethyl 3-methoxymethyl-7-phenoxyacetamido-3-cephem-4carboxylate.

Nuclear Magnetic Resonance spectrum (CDCl3) 8 ppm:=1.25..(9H,. singlet, -t-butyl); 3.35..(3H, singlet, 25 OCH₃); 3.54 (2H, singlet, 2-cephem H₂); 4.29 (2H, singlet, CH2 of methoxymethyl); 4.58 (2H, singlet, (CH2 of phenoxyacetamido); 5.01 (1H, doublet, J=5 Hz, 6cephem H); 5.6-6.1 (3H, multiplet, 7-cephem H and C6H5 and NH).

PREPARATION 2

Pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulfonate

488 mg of phosphorus pentachloride were dissolved in 5 ml of dry methylene chloride, and then 120 mg of phosphorus oxychloride were added to the solution. 40 Whilst the mixture was being stirred at room temperature, 247 mg of pyridine were added. The mixture was then cooled to -10° C., and 769 mg of pivaloyloxvmethyl 3-methoxymethyl-7-phenoxyacetamido-3cephem-4-carboxylate were added thereto. The temper- 45 ature of the mixture was then allowed to rise gradually to room temperature. After stirring the mixture for 2 hours, it was again cooled to 0° C., and then 1.5 ml of propanol were added and the mixture again stirred for 30 minutes. A small amount of water was added to the 50 mixture, which was then stirred for a further 15 minutes. The mixture was diluted with 50 ml of ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate. The ethyl acetate layer was separated and dried over anhydrous magnesium sulphate. 55 The drying agent was filtered off and the filtrate was concentrated by evaporation under reduced pressure. Diisopropyl ether was added to the residue and the wall of the vessel was scraped. The resulting precipitates were collected by filtration and dried to give 443 mg of 60 the desired pivalo-yloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate. This compound was dissolved in 5 ml of ethyl acetate, and then an equimolar amount of p-toluenesulfonic acid monohydrate in 5 ml of ethyl acetate was added to the solution. The resulting 65 mixture was allowed to stand at ambient temperature for 3 hours, affording 523 mg of the title compound melting at 160°-170° C. (with decomposition, recrystal-

lized from methylene chloride and ethyl acetate) in the form of needles.

Elemental Analysis: Calculated for C15H22N2O6S.C1 H₈O₃S: C, 49.80%; N, 5.70%; N, 5.28%; S, 12.08%. 5 Found: C, 49.76%, H, 5.60%; N, 5.00%; S, 12.06%.

PREPARATION 3

Benzhydryl

7-[2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxvlate

To 0.057 ml of dimethylformamide were added 0.061 ml of phosphorus oxychloride, with ice-cooling and stirring. The mixture was then stirred at 40° C. for 1 hour and then twice subjected to azeotropic distillation with dry methylene chloride. 1 ml of ethyl acetate was added to the resulting mixture, which was then vigorously stirred at room temperature whilst 200 mg of 2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetic acid were added. Stirring was continued for a further 30 minutes to give a mixture (a).

Meanwhile, 200 mg of benzhydryl 7-amino-3methoxymethyl-3-cephem-4-carboxylate and 145 mg of N,N-diethylaniline were dissolved in 5 ml of methylene chloride, and the mixture was stirred at -5° C. to give a mixture (b).

Mixture (a) was then added dropwise to mixture (b) and the mixtures were stirred together for 15 minutes, CH2 of pivaloyloxymethyl); 6.7-7.6 (6H, multiplet, 30 after which the resulting reaction mixture was concentrated by evaporation und - educed pressure. 20 ml of ethyl acetate and 5 ml of water were then added to the residue and the ethyl acetate layer was separated. This layer was washed in turn with 5 ml of a saturated aqueous solution of sodium bicarbonate, 5 ml of a 5% w/v aqueous solution of hydrogen chloride and finally 5 ml of a saturated aqueous solution of sodium chloride, after which the solution was dried over anhydrous magnesium sulphate. The drying agent was filtered off and the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was chromatographed through 30 g of silica gel (Kieselgel 60), eluted with a 3:2 by volume mixture of hexane and ethyl acetate, to give 213 mg of the desired benzhydryl 7-[2-(2chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-car-

> Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 3.19 (3H, singlet, OCH₃ of methoxymethyl); 3.51 (2H, singlet, 2-cephem H₂); 4.09 (3H, singlet, OCH₃ of methoxyimino): 4.20 (2H, singlet, CH2 of methoxymethyl); 4.22 (2H, singlet, CH2 of chloroacetamido); 5.02 (1H, doublet, J=5 Hz, 6-cephem H); 5.86 (1H, doubled doublet, J=5 and 9 Hz, 7-cephem H); 6.7-7.6 (12H, multiplet).

boxylate.

PREPARATION 4

7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid trifluoroacetate

200 mg of benzhydryl 7-[2-(2-chloroacetamidothiszol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, followed by 45 mg of thioures, were dissolved in 5 ml of dimethylacetamide. The solution was maintained at room temperature for 2 hours, after which a saturated aqueous solution of sodium bicarbonate was added. The reaction mixture was then extracted with 20 ml of ethyl acetate and the extract was washed with water to remove excess thiourea and then dried over anhydrous magnesium sulphate. After the drying agent had been filtered off, the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was chromatographed through 30 g of silica gel (Wacogel C-100), eluted with ethyl acetate, to afford 63 mg of benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

The whole of this product was dissolved in 2 ml of anisole, and then 1 ml of trifluoroacetic acid was added to the solution, with ice-cooling and stirring. The mixture was then maintained at room temperature for 30 minutes, after which it was concentrated by evaporation under reduced pressure and disopropyl ether was added to the residue. The resulting precipitates were collected by filtration and dried, to afford 27 mg of 7-[2-(2-aminothiazol-4-yl)-2-methoxyminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid trifluoroacetate.

Nuclear Magnetic Resonance spectrum (deuteroacetone/D₂O) δ ppm: 3.29 (3H, singlet, OCH₃ of methoxymethyl); 3.57 (2H, singlet, 2-cephem H₂); 3.96 (3H, singlet, OCH₃ of methoxymino); 4.27 (2H, singlet, CH₂ of methoxymethyl); 5.15 (1H, doublet, J=5.0 Hz, 6-cephem H); 5.97 (1H, doublet, J=5.0 Hz, 7-cephem H); 6.59 (1H, singlet).

PREPARATION 5

7-[2-(2-Chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic scid

A mixture of 7.65 g of benzhydryl 7-[2-(2-chloroacetamidothiazol-4-yl]-2-methox-yiminoacetamido]-3-methoxymethyl-3-cephem-4-car-boxylate, 25 ml of methylene chloride, 5 ml of anisole and 20 ml of trichloroacetic acid was allowed to react at room temperature for 30 minutes. At the end of this time, 300 ml of diisopropyl ether were added to the reacton mixture and the resulting precipitates were 40 collected by filtration, giving 5.95 g of 7-[2-(2-chloroacetamidothiazol-4-yl)-2-methox-yiminoacetamido]-3-methoxymethyl-3-cephem-4-car-boxylic acid.

Nuclear Magnetic Resonance spectrum 45 (deuteroacetone/deuterodimethyl sulphoxide) δ ppm: 3.30 (3H, singlet, OCH₃ of methoxymethyl); 3.60 (2H, singlet, 2-cephem H₂); 3.97 (3H, singlet, OCH₃ of methoxymino); 4.25 (2H, singlet, CH₂ of methoxymethyl); 4.37 (2H, singlet, CH₂ of chloroacetamido); 5.20 (1H, 4.37 (2H, singlet, CH₂ of chloroacetamido); 5.20 (1H, 50 doublet, 6-cephem H); 5.90 (1H, doubled doublet, J=5.0 and 9.0 Hz, 7-cephem H); 7.40 (1H, singlet, 5-thiazole H); 9.50 (1H, doublet, J=9 Hz, 7-cephem NH).

PREPARATION 6

7-[2-(2-Aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylic acid trifluoroacetate

Following the method of Preparation 3, 225 mg of 2-(2-chloroacetamidothiazol-4-yl)-2-ethoxyiminoacetic 60 acid and 200 mg of benzhydryl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate were reacted to give 280 mg of benzhydryl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, in the form of a yellow powder. 65

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.28 (3H, triplet, OCH₂CH₃); 3.17 (3H, singlet, OCH₃); 3.50 (2H, broad singlet, 2-cephem H₂); 4.07

(2H. singlet, CH₂ of methoxymethyl); 4.0-4.5 (4H, multiplet, OCH₂CH₃ and CH₂ of chloroacetamido); 5.07 (1H, doublet, J=5 Hz, 6-cephem H); 5.93 (1H, doubled doublet, J=5 and 9 Hz, 7-cephem H); 6.90 (1H, singlet, 5-thiazole H); 7.06 (1H, singlet, CH of benzhydryl); 7.31 [10H, singlet, (C₆H₅)₂]; 8.10 (1H, doublet, J=9 Hz, 7-cephem NH).

191 mg of this benzhydryl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate were then treated with 40 mg of thiourea, as described in Preparation 4, to give 117 mg of benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, in the form of a pale pink powder, which was then treated with 1.5 ml of trifluoroacetic acid in a mixture of anisole and methylene chloride. When disopropyl ether was added to the mixture, a precipitate was obtained and this was collected by filtration, to give 90 mg of 7-[2-(2-aminothiazol-4-yl)-2-ethoxyminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid trifluoroacetate.

Nuclear Magnetic Resonance spectrum (deuterodimethyl sulphoxide) & ppm: 1.27 (3H, triplet, J=7 Hz, OCH₂CH₃); 3.23 (3H, singlet, OCH₃); 3.53 (2H, singlet, 2-cephem H₂); 4.16 (2H, quartet, J=7 Hz, OCH₂CH₃); 4.20 (2H, singlet, CH₂ of methoxymethyl); 5.15 (1H, doublet, J=5 Hz, 6-cephem H); 5.76 (1H, doubled doublet, J=5 and 9 Hz, 7-cephem H); 6.80 (1H, singlet, 5-thiazole H); 9.70 (1H, doublet, J=9 Hz, 7-cephem NH); 8.5-10.0 (4H, broad multiplet, NH₂ and two COOH).

PREPARATION 7

t-Butyl 3-oxo-4-p-toluenesulphonyloxybutyrate

To 50 ml of dry acetonitrile were added 7.1 g of t-butyl 4-bromo-3-oxobutyrate and 9.45 g of silver p-tol-uenesulphonate, and the mixture was stirred for 3 days at room temperature, whilst shielding it from the light. The reaction mixture was then filtered and the filtrate was concentrated by evaporation in vacuo.

The resulting crystals containing an oily substance were dissolved in ethyl acetate and the insolubles were removed by filtration. The filtrate was concentrated by evaporation in vacuo, to give a brown, oily substance, which was purified by column chromatography through silica gel, eluted with a 4:1 by volume mixture of cyclohexane and ethyl acetate. The resulting colourless, oily substance was recrystallized from a 1:2 by volume mixture of diethyl ether and hexane, to afford 4.5 g of t-butyl 3-oxo-4-p-toluenesulphonyloxybutyrate, in the form of colourless prisms melting at 67°-69° C.

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.43 (9H, singlet, t-butyl); 2.43 (3H, singlet, CH₃ of toluene); 3.43 (2H, singlet, —CH₂COO—); 4.60 (2H, singlet, —SO₂OCH₂—); 7.20-7.90 (4H, C₆H₄).

Elemental Analysis: Calculated for C₁₅H₂₀O₆S: C, 54.92%, H, 6.15%; S, 9.78%. Found: C, 55.03%; H, 6.07%; S, 9.86%.

PREPARATION 8

t-Butyl
2-hydroxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate

4.5 g of t-butyl 3-oxo-4-p-toluenesulphonyloxybutyrate were dissolved in 40 ml of acetic acid, and then 1.42 g of sodium nitrite were added, at room temperature, to 23

the solution over a period of 10 minutes. The mixture was then stirred at room temperature for 50 minutes, after which 200 ml of ethyl acetate were added and the mixture was then washed with an aqueous solution of sodium chloride. The ethyl acetate solution was dried over magnesium sulphate and, after filtering off the drying agent, the filtrate was concentrated by evaporation under reduced pressure to give a brown, oily substance. This oily substance was purified by column chromatography through silica gel, eluted with a 4:1 by volume mixture of cyclohexane and ethyl acetate, affording 1.66 g of t-butyl 2-hydroxyimino-3-oxo-4-ptoluenesulphonyloxybutyrate, in the form of colourless crystals, melting at 106°-108° C. (with decomposition, recrystallized from a 1:1 by volume mixture of diethyl 15

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.52 (9H, singlet, t-butyl); 2.43 (3H, singlet, CH₃ of toluene); 5.04 (2H, singlet, —SO₂OCH₂CO—); 7.20–7.92 (4H, C₆H₄); 10.23 (1H, singlet, OH of hydrox-20

yimino).

ether and petroleum ether).

Elemental Analysis: Calculated for C₁₅H₁₉NO₇S: C, 50.48%; H, 5.36%; N, 3.92%, S, 8.98%. Found: C, 50.62%; H, 5.08%; N, 3.83%; S, 8.97%.

PREPARATION 9

t-Butyl

2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate

To an ice-cooled solution of 1.66 g of t-butyl 2-hydroxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate in 20 ml of dry acetone were added 960 mg of anhydrous potassium carbonate and 0.466 ml oi dimethyl sulphate, and then the mixture was stirred at room temperature for 3 hours. The mixture was then poured into 35 ice-water and extracted with methylene chloride. The extract was washed with an aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated by evaporation under reduced pressure to give a brown, oily substance. This was purified by column 40 chromatography through silica gel, eluted with a 4:1 by wolume mixture of cyclohexane and ethyl acetate, to afford 650 mg of t-butyl 2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrate, as a pale yellow oil.

Nuclear Magnetic Resonance spectrum (COCl₃) 8 45 ppm: 1.50 (9H, singlet, t-butyl); 2.43 (3H, singlet, CH₃ of toluene); 4.07 (3H, singlet, OCH₃); 5.05 (2H, singlet, —SO₂OCH₂CO—); 7.20-7.90 (4H, C₆H₄).

PREPARATION 10

2-Methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyric acid

To a solution of 478 mg of t-butyl 2-(syn)-methox-yimino-3-oxo-4-p-toluenesulphonyloxybutyrate in 1 ml of methylene chloride were added 2 ml of trifluoroacetic acid, and the mixture was stirred at room temperature for 4 hours. The methylene chloride and the excess trifluoroacetic acid were then distilled off in vacuo, leaving a brown, oily substance, which was dissolved in diisopropyl ether and allowed to stand, affording 178 60 mg of 2-(syn)-methoxyimino-3-oxo-4-p-toluenesul-phonyloxybutyric acid, in the form of colourless crystals melting at 131°-132° C. (with decomposition).

Elemental Analysis: Calculated for C₁₂H₁₃NO₇S; C., 45.72%; H, 3.84%; N, 4.45%; S, 10.18%. Found: C, 65.45.50%; H, 3.92%; N, 4.32%; S, 9.88%.

Nuclear Magnetic Resonance spectrum (deuteroacetone) 8ppm: 2.47 (3H, singlet, CH3 of toluene); 4.10 (3H,

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singlet, OCH₃); 5.20 (2H, singlet -SO₂OCH₂CO-); 7.25-7.95 (4H, C₆H₄); 9.80 (1H, broad singlet, COOH).

PREPARATION 11

Pivaloyloxymethyl

7-(2-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate

To a suspension of 464 mg of 2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyric acid in 20 ml of methylene chloride, cooled to -5° C., was added 0.204 ml of triethylamine, and the mixture was stirred for 5 minutes, until completely dissolved. To the resulting solution were added 0.17 ml of oxalyl chloride and a drop of dimethylformamide and the mixture was stirred at -5° C. for 20 minutes. On removing the solvent, there was left 2-(syn)-methoxyimino-3-oxo-4-ptoluenesulphonyloxybutyryl chloride. This was dissolved in 10 ml of methylene chloride, and then 0.394 ml of N,N-diethylaniline, followed by the methylene chloride solution, were added, at -5° C., to a solution of 530 mg of pivaloyloxymethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulphonate in 20 ml of methylene chloride. This mixture was stirred at -5° C. for 5 minutes, after which the solvent was distilled off. The resulting residue was dissolved in ethyl acetate and washed with dilute aqueous hydrochloric acid. The ethyl acetate layer was separated and dried over magnesium sulphate. A' filtering off the drying agent, the filtrate was concentrated by evaporation under reduced pressure, to give a brown, oily substance. This was purified by column chromatography through silica gel eluted with a 4:1 by volume mixture of cyclohexane and ethyl acetate, to afford 510 mg of pivaloy-7-[2-(syn)-methoxyimino-3-oxo-4-ptoluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, in the form of a colourless, foamy substance.

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.22 (9H, singlet, t-butyl); 2.43 (3H, singlet, CH₃ of toluene); 3.30 (3H, singlet, OCH₃ of methoxymethyl); 3.51 (2H, singlet, 2-cephem H₂); 4.10 (3H, singlet, OCH₃ of methoxyimino); 4.27 (2H, singlet, CH₂ of methoxymethyl); 4.97 (1H, doublet, J=5.0 Hz, 6-cephem H₃; 5.07 (2H, singlet, —SO₂OCH₂CO—); 5.53-5.97 (3H, multiplet, 7-cephem H and —OCH₂— of pivaloy-loxymethyl); 7.20-7.93 (5H, multiplet, 7-cephem NH and C₆H₄).

PREPARATION 12

Following the procedure described in Preparation 7, the following compounds were prepared:

t-Butyl 4-methanesulphonyloxy-3-oxobutyrate, as a pale yellow oil.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.47 (9H, singlet, t-butyl); 3.14 (3H, singlet, CH₃SO₂); 3.45 (2H, singlet, —COCH₂CO—); 4.87 (2H, singlet, —SO₂OCH₂CO—).

t-Butyl 4-ethanesulphonyloxy-3-oxobutyrate, a yellow oil.

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.32-1.62 (9H+3H, singlet+triplet, t-butyl+CH₃CH₂SO₂); 3.30 (2H, quartet, J=7.0 Hz, CH₃CH₂SO₂); 3.47 (2H, singlet, —COCH₂CO—); 4.87 (2H, singlet, —SO₂OCH₂CO—).

t-Butyl 4-benzenesulphonyloxy-3-oxobutyrate, clourless needless melting at 94*-96° C.

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.43 (9H, singlet, t-butyl); 3.43 (2H, singlet, —COCH₂CO—); 4.63 (2H, singlet, —SO₂OCH₂CO—); 57.40-8.03 (5H, multiplet, C₆H₅).

PREPARATION 13

Following the procedure described in Preparation 8, the following compounds were prepared:

t-Butyl 2-hydroxyimino-4-methanesulphonyloxy-3-oxobutyrate, white crystals melting at 103°-104° C. (with decomposition).

Nuclear Magnetic Resonance spectrum (CDC1₂/deuteroacetone) & ppm: 1.57 (9H, singlet, t-butyl); 3.20 (3H, singlet, CH₃ of methanesulphonyl); 5.23 (2H, singlet, -SO₂OCH₂CO-); 11.93 (1H, singlet, OH of hydroxymino).

i-Butyl 4-ethanesulphonyloxy-2-hydroxyimino-3oxobutyrate, colourless crystals melting at 85*-87° C. (with decomposition).

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.47 (3H, triplet, J=7.0 Hz, CH₃CH₂SO₂); 1.57 (9H, singlet, f-butyl); 3.33 (2H, quartet, J=7.0 Hz, CH₃CH₂SO₂); 5.23 (2H, singlet, —SO₂OCH₂CO—); 10.50 (1H, singlet, OH of hydroxyimino).

t-Butyl 4-benzenesulphonyloxy-2-hydroxyimino-3oxobutyrate, colourless needles melting at 93°-95° C. (with decomposition).

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.57 (9H, singlet, t-butyl); 5 ° (2H, singlet, -SO-2OCH₂CO-); 7.40-8.03 (5H, multiplet, C₆H₅); 10.17 (1H, broad singlet, OH of hydroxyimino).

PREPARATION 14

Following the procedures described in Preparation 9, the following compounds were prepared:

t-Butyl 4-methanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrate, a colourless oil.

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.54 (9H, singlet, t-butyl); 3.19 (3H, singlet, CH₃ of methanesulphonyl); 4.20 (3H, singlet, OCH₃ of methoxymino); 5.23 (2H, singlet, —SO₂OCH₂CO—).

t-Butyl 4-ethanesulphonyloxy-2-(syn)-methoxyimino- 45 3-oxobutyrate, a pale yellow oil.

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.43 (3H, triplet, J=7.0 Hz,-CH₃CH₂SO₂); 1.50 (9H, singlet, t-butyl); 3.27 (2H, quartet, J=7.0 Hz, CH₃CH₂SO₂); 4.07 (3H, singlet, OCH₃ of methox-yimino); 5.18 (2H, singlet, -SO₂OCH₂CO-).

t-Butyl 4-benzenesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrate, a colourless oil.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.50 (9H, singlet, t-butyl); 4.05 (3H, singlet, OCH₃ 55 of methoxymino); 5.07 (2H, singlet, —SO₂OCH₂CO—); 7.30-8.00 (5H, multiplet, C₆H₅).

PREPARATION 15

Following the procedure described in Preparation 10, 60 the following compounds were prepared:

4-Methanesulphonyloxy-2-(syn)-methoxyimino-3-

oxobutyric acid, a pale brown oil.

Nuclear Magnetic Resonance spectrum (deuteroacetone) 8 ppm: 3.14 (3H, singlet, CH₃ of methanesulphonyl); 4.10 (3H, singlet, OCH₃ of methoxyimino); 5.27 (2H, singlet, —SO₂OCH₂CO—); 10.18 (1H, singlet, COOH).

4-Ethanesulphonyloxy-2-(syn)-methoxyimino-3oxobutyric acid, melting at 85.5°-89° C.

Nuclear Magnetic Resonance spectrum (deuteroacetone) δ ppm: 1.40 (3H, triplet, J=7.0 Hz, CH₃CH₂SO₂); 3.34 (2H, quartet, J=7.0 Hz, CH₃CH₂SO₂); 4.13 (3H, singlet, OCH₃ of methoxyimino); 5.33 (2H, singlet, —SO₂OCH₂CO—); 11.10 (1H, broad singlet, COOH). 4-Benzenesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyric acid, as crystals.

Nuclear Magnetic Resonance spectrum (deuteroacetone) & ppm: 4.06 (3H, singlet, OCH₃ of methoxyimino); 5.17 (2H, singlet, —SO₂OCH₂CO—); 7.37-8.03 (5H, multiplet, C₆H₅); 10.33 (1H, singlet, COOH).

PREPARATION 16

Following the procedure described in Preparation 11, the following compounds were prepared:

Pivaloyloxymethyl 7-[4-methanesulphonyloxy-2-(syn)-methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, a colourless, foamy

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.21 (9H, singlet, t-butyl); 3.16 (3H, singlet, CH₃ of methanesulphonyl); 3.30 (3H, singlet, OCH₃ of methoxymethyl); 3.53 (2H, broad singlet, 2-eephem H₂); 4.13 (3H, singlet, OCH₃ of methoxymino); 4.24 (2H, singlet, CH₂ of methoxymethyl); 4.99 (1H, doublet, J=4.0 Hz, 6-eephem H); 5.23 (2H, singlet, —SO₂OCH₂CO—); 5.60-5.93 (3H, multiplet, 7-eephem H and CH₂ of pivaloyloxymethyl); 7.58 (1H, doublet, J=9.0 Hz, 7-eephem NH).

Pivaloyloxymethyl 7-[4-ethanesulphonyloxy-2-(syn)methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-35 3-cephem-4-carboxylate, a colourless, foamy substance.

Nuclear Magnetic Resonance spectrum (CDC13) 8 ppm: 1.22 (9H, singlet, t-butyl); 1.43 (3H, triplet, J=7.0 Hz, CH3CH2SO2); 3.27 (2H, quartet, J=7.0 Hz, CH3CH2SO2); 3.30 (3H, singlet, OCH3 of methoxymethyl); 3.54 (2H, broad singlet, 2-cephem H2); 4.13 (3H, singlet, OCH3 of methoxymino); 4.26 (2H, singlet, CH2 of methoxymethyl); 5.00 (1H, doublet, J=5.0 Hz, 6-cephem H); 5.27 (2H, singlet, —SO2OCH2CO—); 5.60-5.97 (3H, multiplet, 7-cephem H and CH2 of pivaloyloxymethyl); 7.55 (1H, doublet, J=9.0 Hz, 7-cephem NH).

Pivaloyloxymethyl 7-[4-benzenesulphonyloxy-2-(syn)-methoxymino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, a pale yellow, foamy

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.22 (9H, singlet, t-butyl); 3.30 (3H, singlet, OCH₃ of methoxymethyl); 3.52 (2H, broad singlet, 2-cephem H₂); 4.10 (3H, singlet, OCH₃ of methoxymino); 4.27 (2H, singlet, CH₂ of methoxymethyl); 4.98 (1H, doublet, J=5.0 Hz, 6-cephem H); 5.08 (2H, singlet, —SO₂OCH₂CO—); 5.60-5.90 (3H, multiplet, 7-cephem H and CH₂ of pivaloyloxymethyl); 7.40-8.03 (6H, multiplet, C₆H₅, and 7-cephem NH).

PREPARATION 17

Pivaloyloxymethyl
7-(4-chloro-3-oxobutyrylamino)-3-methoxymethyl-3cephem-4-carboxylate

The second secon

725 mg of diketene were dissolved in 10 ml of dry methylene chloride and the solution stirred at -20° C. 30 ml of a carbon tetrachloride solution containing 620

mg of chlorine were then added dropwise to the solution, to produce 4-chloro-3-oxobutyryl chloride.

Meanwhile, 2 g of pivaloyloxymethyl 7-amino-3methoxymethyl-3-cephem-4-carboxylate p-toluenesulphonate and 1.16 ml of N,N-diethylaniline were dis- 5 solved in 20 ml of methylene chloride. The resulting solution was cooled to -10° C., and then the 4-chloro-3-oxobutyryl chloride solution obtained as described above was added dropwise thereto. The mixture was then stirred at the same temperature for 30 minutes, 10 after which it was concentrated by evaporation under reduced pressure. The resulting residue was dissolved in 50 ml of ethyl acetate and then washed in turn with water, a 5% w/v aqueous solution of hydrogen chloride and an aqueous solution of sodium chloride, after which it was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was dissolved in 3 ml of methylene chloride, and 30 ml of diethyl ether were added thereto, after which the mixture was allowed to stand. The resulting needle-like crystals were collected by filtration. washed with diethyl ether and dried to give 1.47 g of the title compound, melting at 131.5°-132.5° C

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.23 (9H, singlet, t-butyl); 3.31 (3H, singlet, 25 OCH₃); 3.54 (2H, singlet, 2-cephem H₂); 3.65 (2H, singlet, CH₂); 4.26 (2H, singlet, CH₂); 4.29 (2H, singlet, CH₂); 4.97 (1H, doublet, J=5.5 Hz, 6-cephem H); 5.65-6.0 (3H, multiplet, 7-cephem H and CH₂ of pivaloyloxymethyl); 7.64 (1H, doublet, J=9 Hz, 7-30)

cephem NH).

PREPARATION 18

Pivaloyloxymethyl
7-(4-chloro-2-hydroxyimino-3-oxobutyrylamino)-3methoxymethyl-3-cephem-4-carboxylate

2.57 g of pivaloyloxymethyl 7-(4-chloro-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-car-boxylate were dissolved in 25 ml of acetic acid, and then 409 mg of acdium nitrite were added, little by little, at room temperature to the solution, after which the mixture was stirred for 30 minutes. The mixture was then diluted with 200 ml of ethyl acetate, washed three times with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulphate and then 45 concentrated by evaporation under reduced pressure. The residue was twice subjected to azeotropic distillation using toluene and the resulting residue was dried, giving 2.7 g of the title compound as a foamy solid.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 50 ppm: 1.23 (9H, singlet, t-butyl); 3.33 (3H, singlet, OCH₃ of methoxymethyl); 3.59 (2H, singlet, 2-cephem H₂); 4.33 (2H, singlet, CH₂ of methoxymethyl); 4.75 (2H, singlet, CICH₂); 5.05 (1H, doublet, J=5.5 Hz, 6-cephem H); 5.6-6.1 (3H, multiplet, 7-cephem H and CH₂ of pivaloyloxymethyl); 9.3 (1H, doublet, J=9 Hz, 7-

cephem NH).

PREPARATION 19

Pivaloyloxymethyl
7-[4-chloro-2-(syn)-methoxyimino-3-oxobutyrylamino]3-methoxymethyl-3-cephem-4-carboxylate

5g of pivaloyloxymethyl 7-(4-chloro-2-hydroxyimino-3-oxobutyrylamino)-3-methoxymethyl-3-cephem-4-carboxylate were dissolved in 40 ml of tetrahydrofuran. To the resulting solution was added a solution of 2 g of sodium carbonate in 40 ml of water, followed by 5 g of dimethyl sulphate, after which the mixture was

stirred for 30 minutes. The mixture was then diluted with 150 ml of ethyl acetate, and washed twice with each in turn of a saturated aqueous solution of sodium biacarbonate and a saturated aqueous solution of potassium bisulphate, after which it was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was chromatographed through 100 g of silica gel eluted with a 3:1 by volume mixture of chloroform and ethyl acetate, to give a solid containing the title compound. This solid was dissolved in 30 ml of diethyl ether and then left to stand under ice-cooling, to produce crystals, which were washed with diethyl ether and then dried, affording 1.9 g of the title compound as needles melting at 168.5°-169.5° C.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.24 (9H, s nglet, t-butyl); 3.33 (3H, singlet, OCH₃ of methoxymethyl); 3.57 (2H, singlet, 2-cephem H₂); 4.19 (3H, singlet, OCH₃ of methoxyminio); 4.30 (2H, singlet, CH₂ of methoxymethyl); 4.60 (2H, singlet, CICH₂); 5.03 (1H, doublet, J=5.5 Hz, 6-cephem H); 5.6-6.1 (3H, multiplet, 7-cephem H and CH₂ of pivaloy-loxymethyl); 7.19 (1H, doublet, J=9 Hz NH).

PREPARATION 20

Pivaloyloxymethyl
7-[4-chloro-2-(syn)-ethoxyimino-3-oxobutyrylamino]-3methoxymethyl-3-cephem-4-carboxylate

The procedure described in Preparation 19 was repeated, but using diethy, sulphate in place of the dimethyl sulphate. The title compound was obtained in the form of needles melting at 171°-172° C.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.23 (9H, singlet, t-butyl); 1.39 (3H, triplet, J=7 Hz); 3.35 (3H, singlet, OCH₃); 3.57 (2H, singlet, 2-cephem H₂); 4.32 (2H, singlet, CH₂ of methoxymethyl); 4.43 (2H, quartet, J=7 Hz); 4.60 (2H, singlet, ClCH₂); 5.04 (1H, doublet, J=5.5 Hz, 6-cephem H); 5.6-6.1 [3H, multiplet, 7-cephem H and CH₂ of pivaloyloxy-methyl] 7.17 (1H, doublet, J=9 Hz, 7-cephem NH).

PREPARATION 21

Pivaloyloxymethyl 7-[2-(2-formamidothiazol-4-yl)glyoxylamido]-3methoxymethyl-3-cephem-4-carboxylate

To 0.544 ml of N,N-dimethylformamide was added, with ice-cooling, 0.582 ml of phosphorus oxychloride, and the resulting mixture was stirred at 40°-45° C. for 1 hour. The low boiling point materials were removed by allowing the mixture to stand for 5 minutes in vacuo, after which 10 ml of ethyl acetate, 1.25 g of 2-(2-formamidothiazol-4-yl)glyoxylic acid and 3 ml of N,Ndimethylformamide were added, in turn, to the resulting residue at room temperature. The mixture was stirred for 40 minutes and then added to a solution of 2.9 g of pivaloyloxymethyl...7-amino-3-methoxymethyl-3cephem-4-carboxylate p-toluenesulphonate and 2.9 ml of N,N-diethylaniline in 30 ml of methylene chloride at a temperature of -20° C. to -30° C. The mixture was then stirred at 0° C. for 30 minutes, after which it was diluted with chloroform, washed in turn, with an aqueous solution of potassium bisulphite and an aqueous solution of sodium bicarbonate, and then dried over anhydrous magnesium sulphate. The solvent was removed by distillation and the residue was purified by column chromatography through silica gel eluted with 2:1 by volume mixture of ethyl acetate and chloroform, to give 1.9 g of the title compound in the form of an amorphous powder.

Nuclear Magnetic Resonance sepetrum (deuterodimethylsulphoxide) δ ppm: 1.22 (9H, singlet, 5 t-butyl); 3.32 (3H, singlet, OCH₃); 3.57 (2H, broad singlet, 2-cephem H₂) 4.32 (2H, broad singlet, CH₂ of methoxymethyl); 5.07 (1H, singlet, 6-cephem H); 5.7-6.0 (3H, multiplet, —COOCH₂O— and 7-cephem H); 8.03 (1H, broad doublet, J=9 Hz, 7-cephem NH); 8.97 (1H, singlet); 9.05 (1H, broad singlet).

PREPARATION 22

1-Ethoxycarbonyloxyethyl
7-[2-(2-formamidothiazol-4-yl)glyoxylamido]-3methoxymethyl-3-cephem-4-carboxylate

The procedure described in Preparation 21 was repeated, but using 2.8 g of 1-ethoxycarbonyloxyethyl 7-amino-3-methoxymethyl-3-cephem-4-carboxylate p-toluenesulphonate and 1.25 g of 2-(2-formamidothiazol-4-yl)glyoxylic acid, to give 1.5 g of the title compound.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.31 (3H, triplet, J=7 Hz, OCH₂CH₃); 1.59 (3H, doublet, J=6 Hz, CH₃ of carbonyloxyethyl); 3.32 (3H, singlet, OCH₃ of methoxymethyl); 3.56 (2H, broad singlet, 2-cephem H); 4.22 (1H, quartet; J=7 Hz, OCH₂CH₃) 4.32 (2H, singlet, CH₂ of methoxymethyl); 5.03 (1H, doublet, J=5 Hz, 6-cephem H); 6.00 (1H, doubled doublet, J=5+9 Hz, 7-cephem H); 6.7-7.1 (1H, multiplet, CHCH₃); 7.38 (1H, singlet, 5-thiazole H); 8.01 (1H, doublet, J=9 Hz, 7-cephem H); 8.60 (1H, singlet, HCO); 9-12 (broad singlet (HCONH).

EXAMPLE I

Pivaloyloxymethyl
7-[2-(2-aminothiazol-4-yl)-2-methoxyminoacetamido]3-methoxymethyl-3-cephem-4-carboxylate

To 71 mg of dimethylformamide were added, with ice-cooling and stirring, 135 mg of phosphorus oxychloride. The mixture was stirred at 40° C. for 1 hour and then subjected twice to azeotropic distillation using dry methylene chloride. To the resulting mixture was added 1 ml of ethyl acetate, after which, 265 mg of 2-(2-chloroacetamidothiazol-4-yl]-2-methoxyiminoacetic acid were added, with vigorous stirring at room temporature, to the mixture and stirring was continued for

30 minutes.

Meanwhile, 121 mg of pivaloyloxymethyl 7-amino-3methoxymethyl-3-cephem-4-carboxylate and 141 mg of N,N-diethylaniline were dissolved in 5 ml of methylene 50 chloride and stirred at -5° C. The resulting mixture was added dropwise to the mixture containing 2-(2chloroacetamidothiazol-4-yl)-2-methoxyiminoacetic acid prepared as described above. The reaction mixture was stirred for 15 minutes and then concentrated by 55 evaporation under reduced pressure. To the residue were added 20 ml of ethyl acetate and 5 ml of water, and the ethyl acetate layer was separated, washed, in turn, with 5 ml of a saturated aqueous solution of sodium bicarbonate, 5 ml of a 5% w/v aqueous solution of 60 ple 8. hydrogen chloride and 5 ml of a saturated aqueous solution of sodium chloride, and finally dried over anhydrous magnesium sulphate. The drying agent was filtered off and the filtrate was concentrated by evaporation under reduced pressure. The resulting residue 65 was subjected to column chromatography through 10 g of silica gel eluted with a 2:1 by volume mixture of ethyl acetate and hexane, to afford 55 mg of pivaloylox-

ymethyl 7-[2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

This product was dissolved in 1 ml of dimethylacetamide, and 13.5 mg of thiourea were added to the resulting solution, which was then stirred at room temperature for 2 hours. The reaction mixture was then diluted with 20 ml of ethyl acetate, washed with a saturated aqueous solution of sodium bicarbonate and dried over anhydrous magnesium sulphate. The drying agent was filtered off and the filtrate was concentrated by evaporation under reduced pressure. The residue was subjected to column chromatography through 5 g of silica gel eluted with a 3:1 by volume mixture of ethyl acetate and hexane, to afford 36 mg of the title compound.

Nuclear Magnetic Resonance spectrum (deutroacetone) δ ppm: 1.19 (9H, singlet, t-butyl); 3.23 (3H, singlet, OCH₃ of methoxymethyl); 3.52 (2H, singlet, 2-cephem H₂); 3.90 (3H, singlet, OCH₃ of methoxymino); 4.18 (2H, singlet, CH₂ of methoxymethyl); 5.12 (1H, doublet, J=5 Hz, 6-cephem H); 5.8-6.1 (3H, multiplet, 7-cephem H and CH₂ of pivaloyloxymethyl); 6.78 (1H, singlet, 5-thiazole H); 6.6-7.1 (2H, broad singlet, NH₂); 8.01 (1H, doublet, J=9 Hz, 7-cephem NH).

EXAMPLE 2

Following the procedure described in Example 1, the following compounds were prepared:

Acetoxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

Nuclear Magnetic Resonance spectrum (deuteroacetone) δ ppm: 2.10 (3H, singlet, CH₃CO); 3.22 (3H, singlet, OCH₃ of methoxymethyl); 3.52 (2H, singlet, 2-cephem H₂); 3.92 (3H, singlet, OCH₃ of methoxyimino); 4.20 (2H, singlet, CH₂ of methoxymethyl); 5.11 (1H, doublet, J=5 Hz, 6-cephem H); 5.6-6.3 (3H, multiplet, CH₂ of acetoxymethyl and 7-cephem H); 6.76 (1H, singlet, 5-thiazole H); 6.6-7.1 (2H, broad singlet, NH₂); 8.03 (1H, doublet, J=9 Hz, 7-cephem NH).

8.03 (1H, doublet, J=9 Hz, 7-cephem NH).

Isovaleryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyminoacetamido]-3-methoxymethyl-3-cephem-

4-carboxylate

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 0.99 (6H, doublet, J=6.5 Hz, two CH₃ of isovaleryl); 1.3-2.1 (1H, multiplet, CH of isovaleryl); 2.2-2.5 (2H, multiplet, CH₂ of isovaleryl); 3.32 (3H, singlet, OCH₃ of methoxymethyl); 3.56 (2H, broad singlet, 2-cephem H₂); 3.98 (3H, singlet, OCH₃ of methoxymethyl); 5.06 (1H, doublet, J=5.0 Hz,6-cephem H); 5.8 (2H, broad singlet, NH₂); 5.92 (2H, singlet, COOCH₂OCO); 6.08 (1H, doubled doublet, J=5.0 and 9.0 Hz, 7-cephem H); 6.70 (1H, singlet, 5-thiazole H); 8.20 (1H, doublet, J=9.0 Hz, 7-cephem NH).

Pivaloyloxymethyl 7-[2-(2-aminothiazole-4-yl)-2ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4carboxylate, having the properties described in Exam-

EXAMPLE 3

Following the preedure described in Example 1, 1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate was prepared.

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.32 1.30 (3H, triplet, OCH₂CH₃); 1.59 1.61 (3H,

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doublet, CH₃ of carbonyloxyethyl); 3.33 3.32 (3H, singlet, OCH₃ of methoxymethyl); 3.57 (2H, singlet, 2-cephem H₂); 4.03 (3H, singlet, OCH₃ of methoxymino); 4.23 4.21 (2H, quartet, OCH₂C₃); 4.34 4.30 (2H, singlet, CH₂ of methoxymethyl); 5.05 5.10 (1H, doublet, J=5 Hz, 6-cephem H); 5.59 [1H, doubled doublet J=5+9 Hz, 7-cephem H]; 5.73 [2H, broad singlet NH₂]; 6.73 6.70 [1H, singlet, 5-thiazole H]; 6.7-7.1 [1H, multiplet, CH of ethoxycarbonyloxyethyl]; 7.90 [1H, doublet, J=9 Hz, 7-cephem NH].

EXAMPLE 4

Pivaloyloxymethyl
7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]3-methoxymethyl-3-cephem-4-carboxylate

To 10 ml of dimethyl sulphoxide were added 1 g of 7-[2-(2-chloroacetamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid, 380 mg of bromomethyl pivalate and 240 mg of potassium fluoride, after which the mixture was 20 stirred at room temperature for I hour. The mixture was then diluted with 100 ml of ethyl acetate and washed successively with water, a 5% w/v aqueous solution of sodium bicarbonate, a 10% w/v aqueous solution of potassium bisulphate and a saturated aqueous solution 25 of sodium chloride, after which it was dried over anhydrous magnesium sulphate. The solvent was then distilled off under reduced pressure and the resulting residue was subjected to column chromatography through silica gel eluted with a 1:1 by volume mixture of chloro- 30 form and ethyl acetate, to give 300 mg of pivaloyloxymethyl 7-[2-(2-chloroacetamidothiazol-1-yl)-2-(syn)methoxyiminoacetamido]-3-methoxymeth-1-3-cephem-4-carboxylate as a pale yellow powder.

This compound was dissolved, with 60 mg of thio- 35 urea, in 3 ml of dimethylacetamide, and the solution was stirred at room temperature for 4 hours. The mixture was then poured into 10 ml of a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The extract was washed with, in turn, a 10% 40 w/v aqueous solution of potassium bisulphate and a saturated aqueous solution of sodium chloride, after Which it was dried over magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was purified by column chromatography 45 through silica gel eluted with a 3:1 by volume mixture of ethyl acetate and hexane to give 200 mg of the title compound. This compound was identified by nuclear magnetic resonance and found to be identical with the compound obtained in Example 1.

EXAMPLE 5

Isobutyryloxymethyl
7-[2-(2-aminothiazol-4-yl)-2-methoxyminoacetamido]3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 4 was repeated, except that the bromomethyl pivalate was replaced by 360 mg of bromomethyl isobutyrate. There were obtained 180 mg of isobutyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, as a slightly yellow powder.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.20 (6H, doublet, J=6.5 Hz, two CH₃ of isobutyryl); 2.66 (1H, septet, J=6.5 Hz, CH of isobutyryl); 3.21 65 (3H, singlet, OCH₃ of methoxymethyl); 3.40 (2H, AB quartet, 2-cephem H₂); 4.01 (3H, singlet, OCH₃ of methoxymino); 4.16 (2H, singlet, CH₂ of methoxymethyl);

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5.05 (1H, doublet, J=5 Hz, 6-cephem H); 5.6-6.2 (5H, multiplet, NH₂, CH₂ of carbonyloxymethyl and 7-cephem H); 6.65 (1H, singlet, 5-thiazole H); 8.06 (1H, doublet, J=9 Hz, 7-cephem NH).

EXAMPLE 6

Propionyloxymethyl

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 4 was repeated except that the bromomethyl pivalate.was replaced by 340 mg of bromomethyl propionate, to give 165 mg of the title compound as an almost colourless powder.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.17 (3H, triplet, J=6.5 Hz, CH₂CH₃); 2.41 (2H, quartet, J=6.5 Hz, CH₂CH₃); 3.20 (3H, singlet, CH₃ of methoxymethyl); 3.35 (2H, AB quartet, 2-cephem H₂); 4.02 (3H, singlet, OCH₃ of methoxyminio); 4.17 (2H, singlet, CH₂ of methoxymethyl); 5.09 (1H, doublet, J=5 Hz, 6-cephem H); 5.6-6.3 (5H, multiplet, NH₂, CH₂ of carbonyloxymethyl and 7-cephem H); 6.68 (1H, singlet, 5-thiazole H); 8.25 (1H, doublet, J=9 Hz, 7-cephem NH).

EXAMPLE 7

Pivaloyloxymethyl
7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]3-methoxymethyl-3-cephem-4-carboxylate

To a solution of 45 m. I sodium 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (prepared from the corresponding trifluoroacetate) in 1 ml of dimethylacetamide were added, at -15° C., 27 mg of iodomethyl pivalate and the mixture was allowed to react for 15 minutes. At the end of this time, 20 ml of ethyl acetate were added to the reaction mixture, and the mixture was washed, in turn, with water, an aqueous solution of potassium bisulphate and an aqueous solution of sodium bicarbonate. The organic phase was separated and concentrated by evaporation under reduced pressure, and the residue was subjected to column chromatography through silica gel eluted with a 3:1 by volume mixture of ethyl acetate and hexane, to give 49 mg of the title compound, whose properties were identical with those of the compound obtained in Example 1.

EXAMPLE 8

Pivaloyloxymethyl

7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 7 was repeated, except that sodium 7-[2-(2-aminothiazol-4-yl)-2-ethox-yiminoacetamido]—3-methoxymethyl-3-cephem-4-car-boxylate and iodomethyl pivalate were used, to give the title compound.

Nuclear Magnetic Resonance spectrum (CDCl₃) & ppm: 1.22 (9H, singlet, t-butyl); 1.31 (3H, triplet, OCH₂CH₃); 3.30 (3H, singlet, OCH₃ of methoxymethyl); 3.53 (2H, singlet, 2-cephem H₂); 4.28 (2H, quartet, OCH₂CH₃); 4.30 (2H, singlet, CH₂ of methoxymethyl); 5.01 (1H, doublet, J=5 Hz, 6-cephem H); 5.7-6.2 (5H, multiplet, 7-cephem H, NH₂ and CH₂ of carbonyloxymethyl); 6.76 (1H, singlet, 5-thiazole H); 7.70 (1H, doublet, 5=9 Hz, 7-cephem NH).

EXAMPLE 9

1-Ethoxycarbonyloxyethyl
7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate

To a solution of 500 mg of sodium 7-[2-(2-aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate in 5 ml of N,N-dimethylacetamide were added, with ice-cooling, 395 mg of 1-iodoethyl ethylcarbonate, and then the mixture was stirred at room temperature for 30 minutes. At the end of this time, 50 ml of ethyl acetate were added to the reaction mixture, which was then washed with, in turn, 20 ml of water, 20 ml of a saturated aqueous solution of sodium bicarbonate and 20 ml of an aqueous solution of sodium chloride. The mixture was then dried over anhydrous magnesium sulphate and the solvent was removed by distillation under reduced pressure, giving a residue, which was chromatographed through 20 g of 20 silica gel eluted with ethyl acetate, to afford 460 mg of the title compound.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 1.30 (3H, triplet, CH₃CH₂); 1.32 (3H, triplet, CH₃CH₂); 1.59 (3H, doublet, J=6.0 Hz, CH₃ of carbonyloxyethyl); 3.30 (3H, singlet, OCH₃ of methoxymethyl); 3.52 (2H, broad singlet, 2-cephem H₂); 4.22 (2H, quartet, CH₃CH₂); 4.30 (2H, singlet, CH₂ of methoxymethyl); 5.05 (1H, doublet, J=5.0 Hz, 6-cephem H); 5.8 (2H, 30 broad singlet, NH₂); 6.00 (1H, doubled doublet, J=5.0+9.0 Hz, 7-cephem H); 6.75 (1H, singlet, 5-thiazole H); 6.7-7.1 (1H, multiplet, CH resonance arronyloxyethyl); 7.8 (1H, doublet, J=9 Hz, 7-cephem NH).

EXAMPLE 10

Pivaloyloxymethyl
7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]3-methoxymethyl-3-cephem-4-carboxylate

To a solution of 510 mg of pivaloyloxymethyl 7-[2-40] (syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate in 5 ml of ethanol were added 76 mg of thiourea and 84 mg of sodium acetate. 3 ml of water were then added dropwise to the mixture, after which the whole mixture was stirred at room temperature for 3.5 hours. At the end of this time, the ethanol was removed by distillation and the residue was dissolved in ethyl acetate, washed with an aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The ethyl acetate was distilled off, giving a pale brown, foamy substance, which was purified by column chromatography through silica gel eluted with a 2:1 by volume mixture of ethyl acetate and methylene chloride, affording 392 mg of the title compound, in the form of a colourless foamy substance having the same properties as the product of Example 1.

EXAMPLE 11

Propionyloxymethyl
7-[2-(2-aminothiazol-4-yl)-2-methoxyminoacetamido]3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 10 was repeated, but using 490 mg of propionyloxymethyl 7-[2-65 (syn)-methoxymino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-car-boxylate, to give 370 mg of the title compound, having

properties identical with those of the product of Example 6.

EXAMPLE 12

The procedure described in Example 10 was repeated, except that the pivaloyloxymethyl 7-[2-(2-(syn)methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate was replaced by 1-ethoxycarbonyloxyethyl 7-[2-(syn)-methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate or isobutyryloxymethyl 7-[2-(syn)methoxyimino-3-oxo-4-p-toluenesulphonyloxybutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, to give 1-ethoxycarbonyloxyethyl 7-[2-(2aminothiazol-4-yl)-2-methoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate (having properties idential with those of the product of Example 3) and isobutyryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (having properties identical with those of the product of Example 5), respectively.

EXAMPLE 13

The procedure described in Example 10 was repeated, except that 465 mg of pivaloyloxymethyl 7-[4-methanesulphonyloxy-2-(syn)-methoxymino-3-oxobutyrylaminol-3-methoxymethyl-3-cephem-4-car-boxylate and 152 ...g of thiourea were used, to give 390 mg of pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-35 4-carboxylate, having properties identical with those of the product of Example 1.

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The same compound was also obtained following the same procedure, but using, in separate experiments, pivaloyloxymethyl 7-[4-ethanesulphonyloxy-2-(syn)-methoxyminino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate or pivaloyloxymethyl 7-[4-benzenesulphonyloxy-2-(syn)-methoxyminino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate.

EXAMPLE 14

Pivaloyloxymethyl
7-[2-(2-aminothiazol-4-yl)-2-methoxyminoacetamido]3-methoxymethyl-3-cephem-4-carboxylate

47 mg of pivaloyloxymethyl 7-[4-chloro-2-(syn)methoxyimino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate were dissolved in 5 ml of dimethylacetamide and then 14 mg of thioures were added to the solution, which was then stirred at room temperature for 4 hours. The reaction mixture was diluted with 50 ml of ethyl acetate, washed three times, each time with 15 ml of water, dried over anhydrous magnesium sulphate and then concentrated by evaporation under reduced pressure. The resulting residue was dissolved in 1 ml of chloroform, and 20 ml of diisopropyl ether were added to the resulting solution. The precipitate produced was collected by filtration and dried, to give 50 mg of the title compound as a colourless powder having properties identical with those of the product of Example 1.

EXAMPLE 15

Pivaloyloxymethyl
7-[2-(2-aminothiazol-4-yl)-2-ethoxyminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 14 was repeated, except that the pivaloyloxymethyl 7-[4-chloro-2-(syn)-methoxymino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate was replaced by pivaloyloxymethyl 7-[4-chloro-2-(syn)-ethoxymino-3-oxobutyrylamino]-3-methoxymethyl-3-cephem-4-carboxylate, to give the title compound as a colourless powder having properties identical with those of the product of Example 8.

EXAMPLE 16

Pivaloyloxymethyl

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

(a) A solution of 0.25 g of pivaloyloxymethyl 7-[2-(2formamidothiazol-4-yl)glyoxylamido]-3-methoxymethyl-3-cephem-4-carboxylate and 65 mg of methoxyamine hydrochloride in 2 ml of dimethylacetamide was stirred at 40° C. for 140 minutes. At the end of this time, ethyl 25 acetate was added to the reaction mixture, which was then washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed by distillation and the residue was subjected to column chromatography through silica gel, eluted with a 2:1 by volume mixture of ethyl acetate and chloroform, to rive 0.2 g of crude pivaloyloxymethyl 7-[2-(2-formamidothiazol-4-yl)-2-(syn)-methoxyiminoscetamido]-3-methoxymethyl-3cephem-carboxylate, which was further purified by 35 recrystallization from 1 ml of ethyl acetate, to give 170 mg of crystals melting at 172° C. (with decomposition).

Nuclear Magnetic Resonance spectrum (deuterodimethyl sulphoxide) 8 ppm: 1.18 (9H, singlet, t-butyl); 3.22 (3H, singlet, OCH₃ of methoxymethyl); 3.58 (2H, broad singlet, 2-cephem H₂); 3.88 (3H, singlet, OCH₃ of methoxymino); 4.14 (2H, singlet, CH₂ of methoxymethyl); 5.19 (1H, doublet, J=5 Hz, 6-cephem H); 5.82 (3H, multiplet, CH₂ of pivaloyloxymethyl and 7-cephem H); 7.37 (1H, singlet, 5-thiazole H); 8.47 (1H, singlet, HCO); 9.66 (1H, doublet, J=9 Hz, 7-cephem NH); 12.58 (1H, broad singlet, NH of formamido).

(b) To a solution of 2.6 g of the pivaloyloxymethyl 7-[2-(2-formamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate prepared as described above in 72 ml of methanol were added, with ice-cooling, 0.7 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 2.5 hours. The methanol was 55 removed by distillation in vacuo, and then 20 ml each of ethyl acetate and water were added to the residue, after which the mixture was neutralized by the addition of a saturated aqueous solution of sodium bicarbonate. The organic layer was washed with a saturated aqueous 60 solution of sodium chloride, dried and then concentrated by evaporation under reduced pressure. The residue was dissolved in 13 ml of chloroform and the solution was added dropwise, with stirring, to 100 ml of disopropyl ether. The resulting precipitate was col- 65 lected by filtration, to give 2.2 g of the title compound in the form of a colourless powder whose properties were identical with those of the product of Example 1.

EXAMPLE 17

Pivaloyloxymethyl

7-{2-(2-aminothizzol-4-yl)-2-ethoxyiminoacetamido}-3methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 16(a) was repeated, except that the methoxyamine hydrochloride was replaced by 75 mg of ethoxyamine hydrochloride, to give 150 mg of pivaloyloxymethyl 7-[2-(syn)-ethoxymino-2-(2-formamidothiazol-4-yl)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate, in the form of crystals melting at 153° C.

Nuclear Magnetic Resonance spectrum (deuterodimethyl (sulphoxide) 8 ppm: 1.18 (9H, singlet, t-butyl); 1.28 (3H, triplet, OCH₂CH₃); 3.21 (3H, singlet, OCH₃ of methoxymethyl); 3.58 (2H, broad singlet, 2-cephem H₂); 4.15 (2H, singlet, CH₂ of methoxymethyl); 4.19 (2H, quartet, OCH₂CH₃); 5.19 (1H, doublet, J=5 Hz, 6-cephem H); 5.71-5.95 (3H, multiplet, CH₂ of pivaloyloxymethyl and 7-cephem H); 7.38 (1H, singlet, 5-thiazole H); 8.48 (1H, singlet, HCO); 9.64 (1H, doublet, J=8 Hz, 7-cephem NH); 12.60 (1H, broad singlet, NH of formamido).

The procedure described in Example 16(b) was repeated, except that 9.65 g of pivaloyloxymethyl 7-[2-(syn)-ethoxyimino-2-(2-formamidothiazol-4-yl)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate, 170 ml of methanol and 2 ml of concentrated hydrochloric acid were reacted at room temperature for 3 hours, to give 8.7 g of '. title compound in the form of a colourless powder whose properties were identical to those of the product of Example 8.

EXAMPLE 18

1-Ethoxycarbonyloxyethyl
7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]3-methoxymethyl-3-cephem-4-carboxylate

A mixture of 180 mg of 1-ethoxycarbonyloxyethyl 7-[2-(2-formamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate, 5 ml of methanol and 0.05 ml of concentrated hydrochloric acid were reacted as described in Example 16(b), to give 120 mg of the title compound, in the form of a pale yellow powder whose properties were identical with those of the product of Example 3.

EXAMPLE 19

Methoxycarbonyloxymethyl
7-[2-(2-aminothiazol-4-yl)-2-methoxyminoacetamido]3-methoxymethyl-3-cephem-4-carboxylate

To a solution of 500 mg of sodium 7-[2-(2-aminothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate in 5 ml of dimethylacetamide were added, with ice-cooling, 500 mg of iodomethyl methylcarbonate, and the mixture was stirred for 30 minutes. At the end of this time, the reaction mixture was diluted with 50 ml of ethyl acetate, washed, in turn, with a saturated aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The magnesium sulphate was removed by filtration and the filtrate was concentrated by evaporation under reduced pressure. The residue was purified by column chromatography through silica gel, eluted with ethyl acetate, to give 433 mg of the title compound in the form of a foamy substance.

Nuclear Magnetic Resonance spectrum (CDCl₃) 8 ppm: 3.31 (3H, singlet, OCH) of methoxymethyl); 3.56 (2H, broad singlet, 2-cephem H₂); 3.84 (3H, singlet, OCH₃ of methoxycarbonyl); 4.00 (3H, singlet, OCH₃ of methoxyimino); 4.31 (2H, singlet, CH2 of methoxymethyl); 5.05 (1H, doublet, 6-cephem H); 5.5-6.3 (5H, multiplet, 7-cephem H, CH2 of carbonyloxymethyl and NH2); 6.68 (1H, singlet, 5-thiazole H); 8.10 (1H, doublet, J=9.0 Hz, 7-cephem NH).

EXAMPLE 20

Ethoxycarbonyloxymethyl

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

To a solution of 861 mg of sodium 7-[2-(2chloroacetamidothiazol-4-yl]-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate in 8.6 ml of dimethylacetamide were added, at 20 -10° C., 565 mg of iodomethyl ethylcarbonate and the mixture was stirred for 1 hour. At the end of this time, 100 ml of ethyl acetate were added to the reaction mixture, which was then washed, in turn, with water, a 25 saturated aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, and then dried over magnesium sulphate. The organic layer was concentrated by evaporation under reduced pressure and the residue was purified by column chromatography 30 wherein through silica gel eluted with a 2:1 by volume mixture of ethyl acetate and chloroform, to give 696 mg of ethoxycarbonyloxymethyl 7-[4-(2-chloroacetamidothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3methoxymethyl-3-cephem-4-carboxylate.

The whole of this compound was dissolved in 6.4 ml of dimethylacetamide, and 800 mg of thiourea were added to the resulting solution, after which the mixture was stirred at room temperature overnight. The mixture 40 was then diluted with 100 ml of ethyl acetate, washed three times with water and dried over anhydrous magnesium sulphate. The solvent was removed by distillation and the residue was subjected to column chroma- 45 tography through silica gel eluted with ethyl acetate, to give 220 mg of the title compound in the form of a foamy substance.

Nuclear Magnetic Resonance spectrum (CDCl3) & ppm: 1.32 (3H, triplet, J=7 Hz, CH3 of ethoxy); 3.32 50 (3H, singlet, OCH3 of methoxymethyl); 3.53 (2H, broad singlet, 2-cephem H2); 3.98 (3H, singlet, OCH3 of methoxyimino): 4.23 (2H, quartet, J=7 Hz, OCH2CH3); 4.31 (2H, singlet, CH2 of methoxymethyl); 5.04 (1H, doublet, J=6 Hz, 6-cephem H); 5.6-6.3 (5H, multiplet, 7-cephem H, CH2 of carbonyloxymethyl and NH2); 6.63 (1H, singlet, 5-thiazole H); 8.13 (1H, doublet, J=9.0 Hz, 7-cephem NH).

EXAMPLE 21.

Isovaleryloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate

The procedure described in Example 20 was repeated to prepare the title compound, having the same properties as the second compound of Example 2.

EXAMPLE 22

Capsules for oral administration

The following mixture was compounded and enscapulated by conventional means with a No. 2 capsule, to give an encapsulated formulation:

Pivaloyloxymethyl 7-[2-(2-emino-	250 mg
thiazol-4-yl)-2-(syn)-methoxyimino-	
acetamido]-3-methoxymethyl-3-cephem-	
4-carboxylate	
Tale	5 mg
Magnesium stearate	6.7 mg
Sodium laurylsulphate	0.3 mg
Lectore	28 mg

We claim:

1. A compound of the formula

thereof.

R1 is methyl;

R2 is hydrogen o. methyl; and

R3 is a C1-C4 alkoxy;

35 and pharmaceutically acceptable acid addition salts

2. The compound of claim 1 wherein R² is hydrogen.

3. The compound of claim 1 wherein R² is methyl.

4. The compound of claim 1 wherein R³ is ethoxy or ізоргороху.

5. The compound of claim 1 or 2 or 3 wherein R3 is

isopropoxy.

6. The compound of claim 1 which is 1-ethoxycar-7-[2-(2-aminothiazol-4-yl)-2-(syn)bonyloxyethyl methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate and pharmaceutically acceptable acid addition salts thereof.

7. A pharmaceutical composition for oral administration comprising an effective amount of an antibiotic in admixture with a pharmaceutically acceptable carrier or diluent, said antibiotic comprising a compound of the formula

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wherein

R1 is methyl;

R² is hydrogen or methyl;

and

 \mathbb{R}^3 is a \mathbb{C}_1 - \mathbb{C}_4 alkoxy;

and pharmaceutically acceptable acid addition salts thereof.

- 8. The pharmaceutical composition of claim 7 wherein \mathbb{R}^2 is hydrogen.
- 9. The pharmaceutical composition of claim 7 wherein R² is methyl.
- 10. The pharmaceutical composition of claim 7 wherein R³ is ethoxy or isopropoxy.
- 11. The pharmaceutical composition of claim 7 or 8 or 9 wherein \mathbb{R}^3 is isopropoxy.
- 12. The pharmaceutical composition of claim 7 wherein said compound is 1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-car-

boxylate and pharmaceutically acceptable acid addition salts thereof.

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APPENDIX C

Summary of Regulatory Activities

APPENDIX C-1

Summary of Correspondence During IND Period for VANTIN Tablets (Formerly called DOXEF Tablets)

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CONDUCTED BY SANKYO CD., JAPAN, 6/1/87.4

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COMDUCTED BY SANKYO CO., JAPAN, 6/41/87.
EVALUATION OF UTG252 (RSB07) IN THE SALMANSILIA/MICROSOME TEST (AMES-ASSAI) & W#/ESCHERICHIA COLI, C.S. AARON, STUDY COMDUCTED BY SAKKYO CO., JAPAN, 6/10/87.
FORLIMINARY IN VITRO ANTHEACTERIAL EVALUATION OF CS-807 (U76252), SAKKYO'S ORABILY-ACTIVE CEPSALOSPORIN ANTHEOTIC, R.J. TABCE C.E. ZURINGO ET AL 6/19/86.4

G.E. ZURINGO ET AL 6/19/86.4
IN VITRO & IN VIVO EVALUATION OF CS-807 AND RS746 ACAINST BACTERIAL PATHOGENS #OF VETERIBANY INFORMANCE, R.J. TABCE 6/87.# MOTE SUBCUTANDOUS TOXICITY IN MISTAR-IMMICHI RAIS, R.C. PIPER, ET AL, STUDY #CONDUCTED BY SAMIYO CO. JAPAN, 6/3/8 MIKTO CO. JAPAN, 5/2 TUDY CONDUCTED BY SA M DIFFICILE AND ITS PAN, 5/26/874 JAPAN, 6/3/87.4 TOXIN, R.C. PIPER, ET AL STUDI COMBUCIED BAY SANKYO CO. JAPAN, 5/1/ ACUTE INTRAPERITONFAL TOXICITY IN MISTAR-IMMICHI RATS, R.C. PIPER, T JR., ET AL6/23/864

CLINICAL DATA SYSTEM 2.40 LISTING FOR HONDAY, DECEMBER 7, 1992 AT 16:4:16

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RPAGE	1 6A/367	6A/351	6a/332	68/314 68/3 53/351	64/231	i 6x/235	62/203	62/164	1 2/1		5/9	(U76252): EFFECTS ON EXPERIMENTAL INPECTIFON IN A CHC-INDUCED ALL 6#/23/86. AL 6#/23/86. CEFFECTOR ONAL ACT. W/RECARD FP PREVEN. #09 SUBCUTANEOUS ARSC. FORM CEFFECTOR ONAL ACT. W/RECARD FP PREVEN. #09 SUBCUTANEOUS ARSC. FORM TANAPHOUS ABSCESS CAUSED BY STAPHILOCOCCUS EPIDERINDIS, CHFO (U76252): THE THERREDUIL EFFECTS ACAINSTY SYSTEMIC EXPERIMENTAL INFECTS, # ET AL, 5/18/87. 3.C. HANGL, ET AL, 6/2/86.# # (U76252): THE BINDING AFINITIES TO PENICHILIN BINDING PROTEINS OF (U76252): ITS BINDING AFINITIES TO PENICHILIN BINDING PROTEINS OF (U76252): ITS BINDING AFINITIES TO PENICHILIN BINDING PROTEINS OF (U76252): ITS B-LACTANASE STABILITY AND IMMIBITIORY ACTIVITY (SPHECE (U76252): THE EFFECTS OF R-3746 ON THE CRIPCH CRUVE OF BACTERIA (E.)	DING ANT REASONABLE ALTERNATIVES FOR INACTIVE INVESTIGED (16252 AND CEFACIOR IN THE TREATMENT OF COMMUNITY ACCOUNTED (16252 AND CEFACIOR IN THE TREATMENT OF AN ORAL CEPHALOS) FOLERANCE AND PRACACCINETIC STRUDIES OF AN ORAL CEPHALOS) 18. DEGG WILL BE ADMIN ORALLY IN A BANGE OF 100-800 MG.
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CLINICAL DATA SYSTEM LUCI 2.40 LISTING FOR HONDAY, DECEMBER 7, 1992 AT 16:4:16

		_	DESIGNATION NO. 6 "BIOAVAILABILITY CORP OF CEFFOD PROX 200HG TABS HANDTACTURED BEY ROUSEEL DCLAF & FUC 202 1-15 OF T 15 STB OF 4/13/904 "BIOAVAILABILITY CORP OF CEFFOD PROX 200HG TABS HANDTACTURED BEY ROUSEEL DCLAF & FUC 202 1-15 OF T 15 STB OF 4/13/904 "BIOAVAILABILITY CORPOSITION OF DEADLY SPECS: ELSE FOR FCT CEFFODOXINE 100HG # FUC 202 # FULL SPECS: ELSE WO. 46-27 REV 5.02# # FULL SPECS: ELSE WO. 46-27 REV 5.04# # FULL SPECS: ELSE WO. 46-27
RPAGE	22 1 10 11 12 13 2 6/1 - 6/238 6/239 - 6/294 6/1417 - 6/2591		PCT CEPPODOXINE 100MG# # BO# # BO# # IN HOUNDS: EVALUATION OF #50 MG, SARKTO" PROTOCOL R1150-0001 OF TWICE DAILY DOSING OF #3N ORM OF TWICE DAILY DOSING OF #N ORM WHIRE TWICE DAILY ORAL ADMIFNISTRA
PAT TRNUM	7256/89/01.6	7256/89/05/8	SEE P/1140/0036 "BIONVALIABILITY COMP OF CEFTOD PROX 200MG TABS MANUFACTURED BEY ROUSETE DCLAF SEE P/1140/0036 "BIONVALIABILITY COMP OF CEFTOD PROX 200MG TABS MANUFACTURED BEY ROUSETE DCLAF BIS 50M OF 4/13/904 COMP LIST OF COMPONENTS & QUANTIFACTURE COMP OF DRDC, FCT CEFTODOXIME 100MG# † INCREDIENT SPECS FOR FCT CEFTODOXIME 100MG# † INCREDIENT PROCEDURE 700MG TABS MANUFACTURED BY SAUKTO" PROTOCOL R1150-0001 URED BY TUC SECLATIVE TO 100MG TABS MANUFACTURING STUDY OF THEICE DAILY DOSING OF #AN ORAL CEPTAL INCREDIENT VOLUNTEERS" PROTOCOL R1140-4901# INCLIPIE DOSE TOLERANCE AND PHARMACOKINETIC STUDY OF THEICE DAILY DOSING OF #AN ORAL CEPTAL A MULTIPLE DOSE TOLERANCE AND PHARMACOKINETIC STUDY OF THEICE DAILY ORSING OF #AN ORAL CEPTAL A MULTIPLE DOSE PHARMACOKINETICS OF CEFTODOXIME FOLLOWING TWICE DAILY ORAL ADDITIVISERS " **HULTIPLE DOSE PHARMACOKINETICS OF CEFTODOXIME FOLLOWING TWICE DAILY ORAL ADDITIVISERS " **HULTIPLE DOSE PHARMACOKINETICS OF CEFTODOXIME FOLLOWING TWICE DAILY ORAL ADDITIVE OR STABILITY AND COMPONENTS " **ORFOGINETS" ADDITIVE OF TABILITY AND COMPURED #
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- JRB 3-9-90 Amendment 054
 Submitted Item 6 M1140/0002 Puopolo, M/1140/0006 Mullenix,
 Revision M/1140/0004 Libertin, New subinvestigators, M1140/0007
 Tregor study closure, Mark Todd added as a clinical monitor,
 Tregor study closure, Mark Todd added as a Clinical monitor,
 Corrections to previous submissions, Part 8 TR 7228/89/019
 Corrections to previous submissions, Part 8 TR 7228/89/019
 Anés Assay, TR 7224/90/009 Oral Rat, Clinical TR7256/89/081
 HPLC TR 7256/89/030 Protocol 4900 TR 7216/89/054 Protocol
 R/1140/4900
- RWL 3-20-90 Am.endment 055
 Request meeting to discuss whether a computer assisted NDA review system would be useful with NDA
- RED 4-13-90 Amendment 056
 Item 6, P/1140/0036 Hughes, N1140/0001 Phillips. N/1140/0005
 Deeter, N/1140/0006 Koller, Braun, Farber, M/1140/0018 Hooker, N/1140/0004 Amendment Schlossberg, New Subinvestigators, Corrections
- RED 4-12-90 Amendment 057 Item 7 Manufacturing and Control info UPDATE
- RWL 4-5-90 Amendment 058 Confirms meeting of 4-19-90 at 10:00 a.m. per telephone conversations
- JAE 4-20-90
 Request a *preNDA meeting to discuss the content and scope of theNDA, etc.
- RWL 5-16-90 Amendment 59
 Provided prototypes of data displays for screens re
 CANDA per request
 S-17-90 R = 60 000 R + 000 R Read., 0084 New Johnson
 JAE 5-23-90 f61
 Submitted additional info on the Statistical Analysis plans
 In preparation for our Pre-NDA filling meeting on 6-18-90
- JAE 7-6-90 Af63 Submitted revised Efficacy Master Tables as discussed during PraNDA meeting
- JAE 7-6-90 A#62
 Submitted Safety Report from Japan with events serious and unexpected
- JAE 7-10-90 Af65
 Submitted Safety report with event from Japan which was serious and unexpected
 - JAE 7-6-90 Amendment #054
 Submitted Part 6/1-22 Protocol P/1140/0041 Tompkins.
 Protocol M/1140/0001 Rich 6/23-25. Protocol M/1140/0006
 Protocol M/1140/0001 Rich 6/23-25. Part 7/1 Labeling 6/26-30 Bailey; 6/31-41 Amendments, Part 7/1 Labeling for P/1140/0041

7-18-90 RUL Request comments re M/1140/0043, 0044 & 0045 prior to formal submission from Dr. Susan Alpert per

7-25-90 Amendment #067 CPE Submitted Safety Report from Japan where marketed

8-3-90 Amendment #068 JAE Submitted modified tables for review and a brief summary of telephone conversation of 7-17-90

JAE 8-7-90 . Submitted several journal articles we failed to include with our 7-18-90 letter

JAE 8-30-90 A#70 ~ Part 7 1-55 Components, Composition, Stability & Control

9-17-90 A471 JAE × Submitted Annual Report

9-21-90 A#71 JAE ≥ Corrects number of 9-17-90 amendment to #71

CCE 7-20-90 A/66 Submitted Part 6 TR 7256/89/016 Protocol R1140-0001, 6/239-294 TR 7256/89/071 \$1140-4901, 6/295-1416 TR7215/89/058 6/1417-2591 TR7256/89/067 See 2-7-91 Addendum

JAE 11-5-90 -> Ask to submit our tradename to FDA's labeling and Nomenclature

The 11-7-90 New coup Miller, Klimas, Harper, Dennington out Weidenback termination of Weidenback

Submitted Safety Report re case from Japan re tonsilitis & hemorrhagic colitis

JAE 11-21-90 A#76 x Submitted protocol P/1140/0037 & Labeling for M. Alian Tompkins

* Submitted Part 6 Change in Protocol P-1140/0041 M. Allen JAE Tompkins, and adds Herbert A. Hoskow to Protocol N1140/0001

JAE 10-10-90 A#73 Submitted Part 6/1-5 Degelau Protocol P/1140/0046. 6/6 Change in Protocol M1140/0008 Kopel, Kazmierowski, Clower, Tucker, Allen, Stone

12-20-90 A#77 JAE 12-20-90 Af/7 × Submitted IND Safety Report thrombocytosis/w high platelet count

12-21-90 A#78 JAE X Part 6/1-7 Milko Protocol Mil40/0045,, 6/8-11 TR 9165/90/016, 6/12-13 TR 9155/90/024, 6/14-16 TR 7214/90/0007 #172 Prot My40/0046 1-49 Woodruff, 0006 Cury VANTING Tablets, Cespodoxime Proxettl IND 80,254, (name change from Doxcess 4/27/92)

1-3-91 Submitted A#79 Protocol M/1140/0048 1-43, David L. Smith, Protocol M/1140/0045 Mansfield and subs 44-59, Protocol M/1140/0046 Hines & subs 50-62. Moskow & sub 68-65, Stevens 66 -79, Moreno 80-88, Butler 86-65, list of subs for prior protocols, changes in protocols M1140/0004, M1140/0008, M1140/0046, M1140/0037, M1140/0006 Part 7 labeling for Protocol M/1140/0048 pages 100-102

1.9.91 A#80 Submitted Safety Report

1-11-91 Notified that on 11-6-90 we provided FDA with four diskettes containing examples of the type of submission we are planning, Data Base Reference Manual and User Guide & ZyIndex Manual. NDA submission dates is 3-29-91

1-14-91 A#081 Submitted Acute Toxicity Studies: TR's 7227/90/040, 7227/90/042, 7227/90/041, Multi-Dose Toxicity studies TR 7227/90/035, Reproduction Studies TR 7224/90/041, 7224/90/040, Mutagenicity Studies TR 7228/90/061, Other Studies TR 7227/90/043 7227/90/044, Special Toxicity Studies TR 7227/89/071, 7227/89/078, 7227/89/072, 7227/89/084

1-16-91 A#082 Submitted Part 6 TR's 7256/90/032, 1-66; 7215/90/038,67-82; 7256/89/078,83-158; 7215/90/017,157-187; 7256/89/087,188-220; 7215/90/023, 221-247; 7256/89/075,248-292; 7215/90/030,293-309; 7256/90/047,1-54 vol.2; 7215/90/034,55-59; 7256/89/027,70-173; 7215/90/026,174-191; 7215/90/087,192-571

1-18-91 A#83 Submitted TR4 (ADME) 0/1-11 7256/90/073, 6/12-28 7256/90/074, 29-67 7256/87/040, 68-84 7256/90/069, 85-97 7256/90/070, 98-116 7256/90/067, 117-144 7256/90/079, 145-180 7256/90/065, 181-214 7156/87/053, 215-245 7256/90/084, 246-269 7256/88/004, 270-313 7256/90/068, 314-329 7256/90/075, 330-343 7256/90/077, 344-352 7256/90/066, 353-373 7256/90/071, 374-386 7256/90/078, 887-427 7356/90/072, 428-447 7256/90/076, Pharmacology: 448-479 TR 7254/90/076, 480-485 7252/88/013, 486-497 7256/90/076, 498-508 7252/88/049, 509-543 7224/90/055, 544-552 7224/90/056, 553-78 7224/90/057

1-22-91 A#084 Submitted Part 5/1-41 Protocol M/1140/0050, Kearley & subs, Hutchens & subs, Marmorstein, Stone & subs, Rowlands & subs, Weidenbach & subs, Hanna & subs, Hill & subs, Phillips & subs; Protocol M/1140/0001 Weidenbach & subs, Protocol M/1140/0045 Segeall & sub, Gainer & subs, Protocol M/1140/0048 Kamitsuka & sub, Protocol M/1140/0048 Stein & Part 7 Labeling for Protocol M/1140/0050

2-5-91 A#85 Submitted Safety Report of pseudomembranous colitie

2-11-91 A#86 Submitted Part 6/1-11 Protocol M/1140/0048 North, 6/12-26 Stevens, 6/27-31 Protocol M/1140/0050 Collins, 6/32-36 Guerra, 6/37-44 Grambau, 6/45-51 Heatley, 6/52-57 Henkle, 6/58-64 VanHook, 6/65 Change in Protocol M1140/0046 Butler, adds sub Platt to Gipson Protocol M/1140/0002

2-7-91 A#66 Addendum to 7-20-90 to include TR 7215/90/015 Pages 1-636

2-18-91 A#87 Submitted Clinical TR's: 1-40 7214/90/008; 41-60 7256/91-008; 61-85 9155/90/002; 86-139 9155/90/022; 140-183 9155/90/034; 184-287 9155/91/028

8-11-91 A#88 Submitted Clinical TR's: Part 6/1-56, 7214-90-052; 6/57-90, 7215-91-004; 6/91-126, 7256-90-003; 6/127-176, 7256-91-003; 6/170-233, 9156-90-020; 6/234-292, 9155-90-025; 6/293-415, 9155-90-029; 6/416-520, 9155-90-080; 6/521-608, 9155-90-031; 6/604-662, 9155-91-002; Chamistry TR's Part 7/663-698, 7254-90-077; 7/699-706, 7256-89-093; 7/707-721, 7256-90-064; 7/722-739, 7256-90-082; 7/740-763, 7256-91-002; Microglology TR's Part 7/764-780, 7254-90-064; 7/781-795, 7254-90-078; 7/796-810, Microglology TR's Part 7/764-780, 7254-90-064; 7/781-795, 7254-90-078; 7/796-810, 7254-90-074; 7/811-822, 7254-90-075; 7/823-852, 7254-90-078; 7/853-866, 7254-90-079; 7/867-888, 7254-90-080; 7/889-910, 7254-90-081; 7/911-924, 7254-90-082; 7/925-940, 7254-90-083; 7/941-978, 7254-90-084; 7/979-997, 7254-90-085; 7/998-1017, 7254-90-086; 7/1018-1032, 7254-90-087; 7/1033-1039, 7254-90-088; 7/1040-1048, 7254-90-089; 7/1049-1074, 7254-90-090; 7/1075-1098, 7254-90-091; 7/1099-1122, 7254-90-093; 7/1123-1188, 7254-90-094; 7/1189-1202, 7254-90-100

8-13-91 A#89 Submitted Part 6 1-17 Protocol M1140/0001 Butler, 6/18-21 Protocol M/1140/0046 Munoz, Part 6/29-46 Protocol M1140/0048 Norman, 6/47-67 Warron, Part 68-93 Protocol M1140/0060 Chodosh, 6/94-108 Green, 6/109-112 Flatt, 6/113 Change in Protocol M/1140/0050 - addition of numerous sub investigators

5-22-91 A#90 Submitted Part 6 Protocol M/1140/0046 Powell 6/1-6, Protocol M/1140/0050 Chiulli 6/7-12, & Michael S. Bronze 6/13-20

5-28-91 Declare the trade name DOXEF to be unacceptable because of safety issues and another name should be proposed

6-1-91 A#91 Submitted Protocol M/1140/0045 Mechenbier 6/1-4, new subs for 0045 & 0046, M/1140/0050 6/5-12 Allen

7-12-91 A#92 Part 6 Protocol M/1140/0046 Kwa 1-5, Green 6-20, Guerra replaces Moreno & subs

7-25-91 A#98 Submitted Part 6/1-18 Protocol M/1140/0050 Butler, 6/19-24 Amacher & subs, 6/25-80 Zuschke & subs, 6/31-34 Moskow & subs

8-15-91 A#94 Submitted Part 6 New Investigators for Protocol M/1140/004, 6/1-5 Phillips, 6/8-9 McLean, 6/10-14 Stevens, 6/15-18 Knight, 6/19-22 Arthur, 6/23-26 Snyder, 6/27-30 Duke, 6/31-34 Owings, 6/35-38 Mosley, 39-42 Smith Sr., also adds subs to Marmorstein in Protocol M/1140/0050

8-16-91 A#95 Part 6/1-15 Protocol P/1140/0026, Peters & sub, Part 7/19-20 Labeling

8-30-91 A#96 Submitted new investigator to Protocol M/1140/0050 Powell l-8

9-27-91 A#97 Submitted ten Safety Reports which represent cases of colitis

10-25-91 A#98 Submitted Part 6/1-5 Protocol M/1140/0045, Matlock

10-80-91 A#99 Submitted Part 6/1-51 Protocol M/1140/0055, 6/52-60 Turner & 8 subs, Part 7/61-68 Labeling

11-11-91 A#100 Submitted Part 7/1-35 Chemistry/ Mfg/Control

11-18-91 A#101 Submitted new investigator to Protocol M/1140/0048, M/1140/0050, Added Sub-Investigator to Protocol M/1140/0050, and new investigator to M/1140/0046

11-26-91 A#102 Submitted Amendment A to Protocol M/1140/0055 "Evaluation of the Hospital Admission Decision in patients with Community-Acquired Pneumonia" with attachment of a list of investigators who were sent Amendment A.

11-26-91 A#102 Stamped receipt

12-2-91 A#102 Submitted protocol amendment, new investigators (M/1140/0045)
Bushnell, McLean, Murphy, Woehler, Paugh & Tucker - New investigator
(M/1140/0046 Stevens, Tucker - M/1140/0048) Bryant, Adams, Hudson - New
(M/1140/0046 Stevens, Tucker - M/1140/0048) Bryant, Adams, Hudson - New
investigators (M/1140/0065) Melnick, Rosenthal, Snyder, Bittner, Preheim, Gorby,
investigators (M/1140/0065) Melnick, Rosenthal, Snyder, Bittner, Preheim, Bittner, Preheim, Gorby,
investigators (M/1140/0065) Melnick, Rosenthal, Snyder, Bittner, Preheim, Gorby,
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investigators (M/1140/0065) Melnick, Rosenthal, Snyder, Bittner, Preheim, Bittner, Bittner,

12-10-91 A#103 - This letter corrects the cover letter for our 12/2/91 submission which was inadvertently assigned Amendment NO. 109

12-13-91 A#104 Submitted new protocol, P/1140/0057 pages 1 - 13, inv Richard J. Davis and part 7 - chemistry/mfg/control information - labeling

12-31-91 A#105 Submitted Annual Report - This report covers the time period from May 1, 1990 - May 1 - 1991.

1-3-91 A#106 Submitted protocol amendment - relocation of inv M/1140/008 Dr. Barry Carter, added subfine and new investigators M/1140/0054 - Busan Andrew, Ralph Ascher, Marc Lebovits, Anthony Krausen, Robert Ciralsky, Joseph Graboyes, Robert Fiddes, Frederick Harcourt, Paul Jacobsen, Thomas Hansbrough, John Matlock, James Atkins, Jean Murphree, Eugenio Chinea, - New investigator M/1140/0054 William Rodriques, Wahood Khan, Om Chhabra, Tahir Sait, Arthur Guarinello, and Alan Smith

1-21-92 A#107 Submitted New Protocol Amendement P/1140/0040

2-10-91 A#108 Submitted M/1140/0046 New Investigator, Terrance C. Kurts, Co'Inv W. Hadley, Hoyt III, Submitted M/1140/0046 New Investigator Ambriah K. Gupta, Co'Inv Arvind K. Gupta, Submitted M/1140/0048 New Investigator Henry Sneed, Co'Inv Justin Ban, Marie Mitchell, Dennis Zachary, John Heffernan, Charles Korte, Co'Inv Justin Ban, Marie Mitchell, Dennis Zachary, John Heffernan, Charles Korte, James Brown, Tim Wochl, Julie Van Beek, Chris White, Submitted M/1140/0048 New Investigator William G. Moseley, Co'Inv D. Howard Lowe, Marianne G. Rochester, Investigator William G. Moseley, Co'Inv D. Howard Lowe, Marianne G. Rochester, Submitted M/1140/0048 New Investigator Thompson H. Southwell, Co'Inv Dewey R. Heetderks. Barnett, Philip T. Hoekstra, Richard J. Kahnoski, Submitted M/1140/0055 New Investigator R. Brooks Gainer, Co'Inv Charlene F. Horan, Norval L. Rasmusson, Edward T. Blume, Robert Curtis and Timothy Nelms. Submitted Amendment A to Protocol M/1140/0055, an optional addition to the protocol for the attending physician to analyse reasons for hospitalisation.

3-8-92 A#109 - New investigator to previously submitted protocol M/1140/0048, James E. Clark, MD with sub/inv. George L. Stark, MD. Also addition of sub/inv. to previously submitted protocol M/1140/0048 for Dr. Dean Norman's study, Mira Cantrell, MD and Andrew S. Chan, MD. and addition of sub/inv added to Donald S. North's study, protocol M/1140/0048, John J. Redington, MD. Change in Protocol M/1140/0055, provides an opportunity to analyze the reasons for hospitalization by the attending physician. New investigators to a previously submitted protocol, Dr. Leonard Berkowitz replaces Dr. Melanie Maslow as principal investigator with sub/inv Steven Barry, MD and Homer Martinez, Md. Also investigator David M. Parenti, MD with sub/inv. Gary L. Simon, MD and Carmelita U. Tuazon, MD. Addition of sub/inv. to a previously submitted protocol M/1140/0055 Hieu T. Nguyen, MD.

5-13-92 A#110 - Amending the IND to include the following information Clinical (TR 7215/91/025, TR 7215/91/015, TR 7254/90/100, TR 9155/91/006, TR 9155/91/004, TR 9155/90/039)

7-27-92 A# 111 - Submitted new investigator & change in Protocol (M/1140/0055) - new investigator to a previously submitted protocol M/1140/0055, Christopher J. Sullivan, M.D. and subinvestigator, Keith Henry, M.D., Kent Crossley, M.D. Amendment A, protocol M/1140/0055, is an optional addition to the protocol. It provides an opportunity to analyse the reasons for hospitalization by the attending physician.

8-21-92 A# 112 - Submitted new protocol M/1140/0062, "Comparison of Oral Cefpodoxime Proxetil (VANTIN® Tablets) vs Cefaclor (Ceclor®) iin the Treatment of Lower Respiratory Tract Infections". New investigator Avinash Patwardhan, M.D. Submitted new labeling.

9-3-92 A# 113 - Submitted Information Amendment Clinical (TR 7215-92-017) "The Effect of Food on Absorption of Cespodoxime Proxetil Tablets after a 400-mg Dose (Protocol P/1140/0028).

9-8-92 A#114 - Submitted Information Amendment - Part 7 - Chemistry/Mig/Control, updated stability data

9-14-92 A#115 - Submitted Protocool Amendment, new protocol - M/1140/0063 with new investigator David a. McKinsey, MD. Submitted labeling to Protocol M/1140/0063

9-29-92 A#116 - Submitted Annual Report. This report covers the time period from May 2, 1991 - May 1, 1992.

10-19-92 A#115 Addendum · Cover letter of dated 9-14-92 inadvariantly listed David s. McKinsey, MD, as the primary investigator for Protocol M/1140/00633. The primary investigator for the study is David L. Smith, MD.

10-23-92 A#117 - Added subinvestigators to Dr. Marvin J. Bittner's study, Protocol M/11140/0055: Edward A. Dominquez, MD, Andrea M. Prevan, MD, Mark B. Rupp, MD. Added subinvestigator to Dr. Joseph R. Lentino's study: Vijay V. Yeldandi, MD. Added new investigator to a previously submitted protocol M/1140/0055: Bruce S. Ribner, MD and subinvestigator: India J. Burton, MD. Added new investigator to a previously submitted protocol M/1140/0063: Joseph S. Bertino, Jr., Pharm D and previously submitted protocol M/1140/0063: Joseph S. Bertino, Jr., Pharm D and subinvestigators: Anne N. Nafziger, MD, MHS Michael Foltzer, MD, Caterine Pulso, Rn, Linda Stragand, BSN, BS

11-6-92 - Submitted Protocol Amendment, New Investigator to a previously submitted protocol M/1140/0048 1/8/91 - DDan Osterweil, MD with subinvestigators: Carmen Lamp, Pharm. D. and Loretta Mazorra, RNC, MN,GNP. New Investigator to previously submitted protocol M/1140/0063 on 9/14/92 - John V Temte, MD, PhD with subinvestigator: John Phylis, RPh. New Investigator: Melamie J. Maslow, MD with subinvestigator Waref Armeh, MD and Adriana Vasquez, MD. New Investigator to subinvestigator Waref Armeh, MD and Adriana Vasquez, MD. New Investigator to previously submitted Protocol M/1140/0055 on 10/30/91 - John F Toney, MD and subinvestigator Douglas Holt, MD and John Groene, MD

APPENDIX C-2

Summary of Correspondence During IND for VANTIN Granules (Formerly called DOXEF Granules)

4-30-92 - A#4 - AS a result of a scale-up of this product to production size equipment, it was decided that minor revisions should be made in Item 3. Production lot size, adjustment in the excipient ranges for the amount of Opadry applied, change in order of mixing binder solution components, identification debossed on tablet, removal of in-process control test for film coated tablet moisture.

5-28-92 A#5 - Submitted updated stability data for VANTIN Tablets. Current data on 18 months at room temperature and ambient room temperature, and 12 months at accelerated conditions support a 24 month expiration dating for product packaged in the container-closure systems described in the NDA.

6-2-92 - We are in receipt of the FDA May 7, 1992 review of the Environmental Assessments for VANTING Tablets, NDA 50-674 and VANTING for Oral Suspension, NDA 50-675. We have listed the FDA comments with our response. This information responds to all deficiencies listed in the May 7 review.

6-9-92 - Provided the following information in response to requests made from June 5, 1992 telephone discussion with Jeff Mehring, Upjohn: 1) Calculations pertaining to environmental concentrations of released substances are shown in Section 8. This includes a calculation for the MEEC. 2) An additional summary table for environmmental parameters.

6-15-92 - Submitted revisions in the package insert doe VANTIN Tablets and Oral Suspension as requested in the FDA review dated March 23, 1992.

6-17-92 - acknowledged receipt

6-16-92 - Notified FDA we had misnumbered two amendments, Amendment No. 4 dated 4-30-92 should be No. 5 & Amendment No. 5 dated 5-28-92 should be No. 6 6-17-92 - acknowledged receipt

6-23-92 - Submitted inserts for distribution in countries other than the United States per FDA request

6-23-92 - Letter to Jerry Abramson, Ph.D., FDA - reference to Item #1 Sankyo has not been assigned a DMF number by the FDA

6-30-92 - Submitted a copy of the cefpoduxima proxetil Environmental Assessment which may be released under Freedom of Information. This fulfills the commitment made in our letter dated June 2, 1992.

7-01-92 - FDA ack'd receipt

7-2-92 - Resubmitted a copy of the cofpodoxime proxetil Environmental Assessment which may be released under Freedom of Information. MSDSs in Item 15 have been replaced with itemized charts.

12-19-91 Submitted revised Microbiology Section in package insert as FDA suggested in fax of 8-14-91 except for retaining "(including penicillinase- and non-penicillinase producing strains)"

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- 1-15-92 Submitted safety update report (see 2 separate volumes)
 1-15-92 FDA acknowledged receipt
- 1-30-91 Submitted draft CFR monographs
- 2-10-92 Per telephone discussion of last week, we set the TosoHaas column (Number 8TIM4987 for validation of T/A 1675
- 2-12-92 A#3 Submitted completed environmental assessment 2-13-92 Ack'd receipt
- 3-2-92 Response to fax dated 2/21/92 we supplied the following information: Solubility/pH profile for cefpodoxime proxetil, and Assay validation and UV spectrum for cefpodoxime proxetil in dissolution medium.
- 3-10-92 Provided responses to the deficiencies in the Control/Manufacturing section of the NDA
- 3-12-92 A#4 Submitted technical Report #7215-92-006 entitled Bioequivalence Study of a Clinical Lot and a Production Lot of Cefpodoxime Proxetil Tablets (Protocol P/1140/0040)
- 3-25-92 Addendum to A#3, per request of Dr. Phillip Vincent all raw data is submitted in 7 volumes. Only one archival copy will be submitted to each NDA per telephone conversation with Ms Peter Dionne
- 3-31-92 We are revising the Microbiology section of the cefpodoxime proxetil tablets and oral suspension insert to include the following statement in the second sentence of the first paragraph: "Cefpodoxime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins, due to the presence of beta-lactamases, may be susceptible to cefpodoxime.
- 4-8-92 Submitted CMC section of Item 3 "Chemistry-Manufacturing-Control"
- 4-16-92 Provided responses to telephone request of 3-26-92

Cefpodoxima Proxetil Tablets (DOXEF®) NDA 50-674 (Name changed to VANTING 4-27-92)

3-29-91 Submitted original NDA

- 5-3-91 Ack. assigns number and states filing date will be 6-
- 8-13-91 Received fax of the deficiencies in the CMC sections
- 8-15-91 Received a copy of the Microbiology Section review
- 3-6-92 extension of FDA review time to 6/29/92
- 8-7-92 NDA 50-674 and 50-675 are approved effective as of the date of this letter
- 4-16-91 Notifies FDA that we will deliver equipment to review the Chemistry-Manufacturing-Control sections on 4-18-91 (optical drive, etc.)
- 5-14-91 Submitted samples for assay methods validation per request of FDA
- 5-20-91 Submitted corrected pages for TR 9156/91/005 5-21-91 Ack'd receipt
- 5-29-91 Submitted components and values of the work station delivered to Dr. Susan Alpert on 5-2-91
- 7-11-91 Lists TUC personnel and issues for discussion for 7-17-91 meeting 7-11-91 Ack'd receipt
- 7-26-91 Submitted 5 protocols prior to beginning the testing program per meeting of 7-17-91
 - 8-29-91 FDA will accept release of bulk on basis of Sankyo assay. TUC must perform all tests on first 3 lots and every 10th lot thereafter
- 9-20-91 Submitted A#1 Safety update, 8.1-1.10 including revised Integrated Summary of Safety and appropriate tables (Mary still has this submission)
 - 10-1-91 Consider a major amendment and have determined that 180 additional days will be required for its review. New date is 3-14-92
- 10-4-91 We are providing two copies of domestic pivotal study protocols and lists of investigators per request (2 volumes)
- 11-11-91 Submitted Environmental Assessment information prepared for inclusion in Sankyo DMF

8-17-92 - Letter to FDA from Kathleen J. Day enclosing press kit for VANTING Oral Suspension and Tablets. A copy of final labeling is also provided. 8-31-92 - FDA recommends eliminating use of *extended

spectrum" or any comparable claim.

8-19-92 - Letter to FDA from Kathleen J. Day enclosing core introductory promotional matierials for VANTING Oral Suspension and Tablets to be used at market launch in October 1992.

9-17-92 - FDA comments and/or recommendations on Primmary Care Introductory Ad and Comprehensive Detailer

9-3-92 - Sent under separate ocover five volumes of data to Marie Bouton, PhD, Roussel UCLAF, Inc. Paris, France which were submitted to the FDA on August 11, 1992.

9-4-92 - Letter to Tatsuo Haneishi, PhD, Deputy Director of Sankyo Company, Ltd informing of the five volume supplement to the VANTIN Tablets New Drug Application.

9-10-92 - Submitted missinig pages 350-378 from Volume 1 of Supplement 8-0001, use in bronchitis.

9-17-92 - Letter to FDA stating that we have been informed by Sankyo, Co., Ltd., Tokyo, Japan, that Amendment No. 5 was submitted to their Drug Master File (no number assigned) on August 28, 1992.

9-29-92 - Per request on the August 7, 1992 approval letter we are supplying the FDA one bottle and carton for VANTIN Tablets 100mg and VANTIN for Oral Suspension 100 mg/5 ml.

9-30-92 - Submitted USX7703.00 Value Added Folder (refer to submission of 9/23/92 on Form 2253 for NDA 18-766 for ANSAID® Tablets), USX6399.00 - Borin Reprint, USX6401.00 Dumont Reprint, USX758C.00 Trial Program Enrollment Form, USX6947.00 Indications and Dosage Guide and package insert code 5R2105/1

10-6-92 - Letter from Rathleen J. Day to FDA sending the final revised copy of the introductory multi-disease presenter for VANTING Oral Suspension and Tablets, USX6406.00.

10-6-92 - Letter from Mathleen J. Day to FDA sending final revised copies of introductory promotional materials for VANTING Oral Suspension and Tablets.

10-13-92 - Letter to Dr. Lumpkin, MD, TUC is aware that the data with Dr. Susan Alpert plans to use in her presentation of the CANDAR to the Pharmaceutical Manuufacturers Association is releasable under Freedom of Information.

11-6-92 - Expedited Review, Submitted a revised package insert for VANTING Tablets and Oral Suspension to delete agranulocytosis and pancytopenia as Laboratoory Chhanges occurring in pediatric patients.

11-12-92 - FDA acknowledged receipt of 11-9-92, supplement number 8-002

11-13-92 - Submitted Brochures USX6393.00, USX6437.00, USX6406.00, USX7661.00, File Cards USX6394.00, Price List USX6413.00, Promotional Letters USD6414.00, USD6416.00, USD6415.00, Literature Reprint USX6402.00, USX7785.00, Other Materials USX7350.00, USX7489.00, USD7800.00 and Package Insert 5R2105/1

11-25-92 - Submitted Brochures USX6395.00, USX7349.00 and USX6397.00, Promotional letters USD7577.00, USD7698.00, USD7700.00, USD7581.00, USD7699.00, USD7871.00 and other materials USD6408.00 and USX7578.00 and package insert 5R 2105-1

APPENDIX C-3

Summary of Correspondence During NDA for VANTIN Tablets (Formerly called DOXEF Tablets)

CLIBICAL DATA SYSTEM LUCI 2.40 LISTING FOR MONDAY, DECIMBER 7, 1992 AT 15:44:39

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CLIMICAL DATA SYSTEM LUCI 2.40 LISTING FOR HONDAY, DECEMBER 7, 1992 AT 15:44:39

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THE STREPTOCOCCAL PHARYNCIFIS/TONSILLITS #IN INFANTS & CHILDRESS SUB 9/6/89 PG 1/319

SEE N/1140/0028 "COMP OF CEPPOD PROX 0 SUSP (100MG/5ML) & PENICILLIN WS POTASSIFUM 0 SUSP (250MG/5ML) IN TRIBBT OF A THE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS #IN INFANTS & CHILDREN" SUB 9/6/89 PG 1/319

SEE N/1140/0028 "COMP OF CEPPOD PROX 0 SUSP (100MG/5ML) & PENICILLIN WS POTASSIFUM 0 SUSP (250MG/5ML) IN TRIBBT OF A CUTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS# IN INFANTS & CHILDREN" SUB 9/6/89 PG 1/319

SEE N/1140/0028 "COMP OF CEPPOD PROX 0 SUSP (100MG/5ML) & PENICILLIN WS POTASSIFUM 0 SUSP (250MG/5ML) IN TRIBBT OF A SUB N/1140/0028 "COMP OF CEPPOD PROX 0 SUSP (100MG/5ML) & PENICILLIN WS POTASSIFUM 0 SUSP (250MG/5ML) IN TRIBBT OF CUTE STREPTOCOCCAL PHARYNGITIS/TONSILLITIS# IN IMPANTS & CHILDREN" SUB 9/6/89 PG 1/319

CUTE STREPTOCOCCAL PHARYNGITIS/TONSILLIT# IN IMPANTS & CHILDREN" SUB 9/6/89 PG 1/319

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CLINICAL DATA SYSTEM LUCI 2.40 LISTING FOR BONDAY, DECEMBER 7, 1992 AT 15:44:39

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PAT TREWN	112	113	- I	S :	9 9 - 1	<u> 63</u>	19	3 5 (05	66 <u> </u>	31	(100MC/SML) VS AMOX/CLL #6/89 ORIG SUB PG 1/16: P(100MC/SML) VS TRIPETI SUB 9/6/89 ORIG SUB 1/1 #/6/89 ORIG SUB PG 1/1 EP(100MC/SML) VS TRIPETI #B 9/6/89 ORIG SUB PG 1100MC/SML) & PENICILLIN 14 CHILDERN SUB 9/6/89 145. CHILD" SUB 9/6/89	100EC/5EL) VS BACTALM 100EC/5EL) VS BACTALM 1NTAMTS & CHILD" SUB-	(100RG/SEL) G 1/163 ORI((100RG/SEL) H 9/6/89 OR
SDATE	10/24/89	10/24/89	10/24/89	10/24/89	11/ 2/89	11/ 2/89	11/ 2/89	11/ 2/89	11/ 2/89	11/ 2/89	11/ 2/89		SEE M/1140/0020-COMP OF CEFPOD PROX OSUSP SEE M/1140/0020-COMP OF CRIPCO PROX OSUSP SEE M/1140/0020-COMP OF CRIPCO PROX OSUSP SEE M/1140/0020-COMP OF URINARY TRACT INFECTS INF	COMP OF CEFFOD PROX OF CEFFOR PROX O
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CLINICAL DATA SYSTEM LDCI 2.40 LISTING POR MONDAY, DECEMBER 7, 1992 AT 15:44:39

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MAILAD/O013 "COMP OF CEPPOD PROX OSCURP (100MG/SML) VS ADGRENTIN GENER (1250\$MG/ML) IN TRETARY OF ACUTE SUPPONDED WITH SECURIAL AND INVESTMENTS & CHILD. SUB 9/6/89 ORIG SUB PC 1/163 MAILAD/O013 "COMP OF CEPPOD PROX GENER (100MG/SML) VS ADGRENTIN OSCURP 259MG/ML, IN TRETARY OF ACUTE SUPPONDED WITH SECURATION OSCURP (100MG/SML) VS ADGRENTIN OSCURP (100MG/SML) IN THE TREPHY OF ACUTE SUB-MAILADOVOLO "COMP OF CERPOD PROX OSCURP (100MG/SML) VS ADGRENTIN OSCURP (100MG/SML) VS ADGR		4	¥ 	O.	
COMP OF CERPOD PROX OSCURP (10046/54L) VS AUGMENTIN CENTER (12046/12) IN TRIBANTS & CHILD SUB 9/64/89 ORIG SUB PG 1/163 IN INVANTS & CHILD* SUB 9/64/89 ORIG SUB PG 1/163 IN INVANTS & CHILD* SUB 9/64/89 ORIG SUB PG 1/163 IN INVANTS & CHILD* SUB 9/64/89 ORIG SUB PG 1/163 IN INVANTS & CHILD* SUB 9/64/89 ORIG SUB PG 1/163 IN INVANTS & CHILD* SUB 9/64/89 ORIG SUB PG 1/163 IN INVANTS PROX OSCURP (10046/54L) VS AUGMENTIN OSCURP (10046/64L) IN THE TRIBAT OF ACUTE SUB PC 1/166 INCOMP OF CERPOD PROX OSCURP 10046/54L VS BACTRIN OSCURP (2504/6/44L) IN THE TRIBAT OF ACUTE SUB PC 1/163 INCOMP OF CERPOD PROX OSCURP 10046/54L VS BACTRIN OSCURP (2504/6/44L) IN THE TRIBAT OF ACUTE SUB PC 1/163 INCOMP OF CERPOD PROX OSCURP 10046/54L VS BACTRIN OSCURP (2504/6/44L) IN THE CONG SULFAMETHONARD (10046/54L) IN INFANTS & CHILD* SUB 9/6/89 ORIG SUB PC 1/266 "COMP OF CERPOD PROX OSCURP 10046/54L & PRACTLIAN V POF CSURP# (2504/6/54L) IN TRIBAT OF ACUTE SUB PC 1/260 ORIG SUBPRINT OF ACUTE SUBPRICED PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF ACUTE SUBPRICED PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF ACUTE SUBPRICED OF PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF ACUTE SUBPRICED OF PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF ACUTE SUBPRICED OF CERPOD PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF ACUTE SUBPRICED OF CERPOD PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF CREPOD PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF ACUTE SUBPRICED OF CERPOD PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF CREPOD PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF CREPOD PROX OSCURP (10046/54L) & PRHICILLIN V POF CSURP# (25046/54L) IN TRIBAT OF CHILD* (25046/54L)	z				
*COMP OF CEFFOR PROX CSUSF (100MG/SML) TANDERNIN GEOSP 250MG/ML IN TRIMET OF ACUTE SUFF OTITIONAL IN INFARTS 4 CHILD SUB \$9/6/89 CRIG SUB PC 1/163 3 "COMP OF CRFPOR PROX CSUSF (100MG/SML) VS AUGHENTIN GEOSP 40MGFTHIMETHOPRIN 6 10MG SULFAMETHOXAGO 4 COMP OF CRFPOR PROX CSUSP (100MG/SML) VS AUGHENTIN GEOSP (250MG/ML) IN THE TRIMET OF ACUTE SUB- 5 "COMP OF CRFPOR PROX CSUSP (100MG/SML) VS AUGHENTIN GEOSP (250MG/ML) IN THE TRIMET OF ACUTE SUB- 6 "COMP OF CRFPOR PROX CSUSP (100MG/SML) VS AUGHENTIN GEOSP (250MG/ML) IN THE TRIMETHOXAGO 7 "COMP OF CRFPOR PROX CSUSP (100MG/SML) VS BACTRIM SSUSP 40MG TRIMETHOPRIN 6 100MG SULFAMETHOXAGO 8 "COMP OF CRFPOR PROX CSUSP (100MG/SML) VS BACTRIM SSUSP 40MG TRIMETHOPRIN 6 100MG SULFAMETHOXAGO 9 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 10 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 11 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 12 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 13 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 14 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 15 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 16 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 17 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 18 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 18 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 18 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 18 "COMP OF CRFPOR PROX CSUSP (100MG/SML) & PRINCILLIN V POT CSUSP\$ (120MG/SML) IN TRIMET OF ACUTE 18 "COM	M/1140/		PANTS (REPOD PROX	ORAL SUSP (\$250MG/ML) IN TRIBUT
COX OSUSE (100 MZ) JEST (100 M	11140/	' ~ 5	E OF C	EFFOD PROX	OSUSP(100MG/SML) VS ADMINIATION SONSP 250MGF/ML IN TRIMENT OF ACUTE SURP
"COME OF CEPPOD PROX OSUBP 100M=175ML" IN INFANTS & CHILD" SUB 9/6/89 ORIG SUB PC 1/266 UNCCAP URLEART TRACT INFECHTS IN INFANTS & CHILD" SUB 9/6/89 ORIG SUB PC 1/266 UNCCAP URLEART TRACT INFECHTS IN INFANTS & CHILD" SUB 9/6/89 ORIG SUB PC 1/266 "COME OF CEPPOD PROX OSUSP 100MG/5ML VS BACTRIM OSUSP 40MG TRIPHETHOPRIM & 200MG SULPAMBTHONAGO UNCOME URLE TRACT INFECHTS #IN INFANTS & CHILD" SUB 9/6/89 PG 1/266 ORIG SUB PC 1/266 "COME OF CEPPOD PROX OSUSP 100MG/5ML VS BACTRIM SSUSP 40MG TRIPHETHOPRIM & 200MG SULPAMBTHONAGO UNCOME URLEATE TRACT INFECHTS #IN INFANTS & CHILD" SUB 9/6/89 ORIG SUB P(4/89 PG 1/266 ORIG SUB PC 1/266 ORIG SUB	M/1140/	0013 "COI	TIO SE	BFFOD PROX UB 9/6/89 C	(10005) 251.1 (1000) 11.1 (100
"COMP OF CREPON PROX OSUSP (100MG/JAML) AS ADDITIONAL COMPONENTIAL E 200MG SULPAMETHONAZO MEANTS & CHILD" SUB 9/6/89 PORIG SUB PRACT INTECT NET SUB 9/6/89 PORIG SUB PE 1/266 ORIG SUB PE 1/266 CHILD" SUB 9/6/89 ORIG SUB PE 1/266 ORIG SUB PE 1/260 ORIGE SUB	H/1140/		A OF C	BPPOD PROX	TE IN INFANTS & CHILD SUB 9/6/89 ORIG SU
MEDIA IN LINEAR CORP. CERPOD PROX OSUSP 100MG/5ML VS BACTRIM. SUB 9/6/89 ORIG SUB PG 1/266 M/1140/0020 "CORP OF CERPOD PROX OSUSP 100MG/5ML VS BACTRIM SSUSP 40MG TRI\$METHOPRIM & 200MG SUILFAMETHONASO IN PERMIT OF UNCOME URIBARY TRACT INFECTES \$1M INFANTS & CHILD. SUB 9/6/89 PG 1/266 ORIG SUB M/1140/0020 "COMP OF CERPOD PROX OSUSP 1100MG/5ML) & PENICILLIN V POT OSUSP\$ (1250MG/5ML) IN FETMET OF ACUTE OCCAL PHARMACITIS/TOMSILLINIS IN INFANT\$ & CHILD. SUB 9/6/89 ORIG SUB PG 1/319 M/1140/0028 "COMP OF CERPOD PROX OSUSP (100MG/5ML) & PENICILLIN V POT OSUSP\$ (250MG/5ML) IN INFANT\$ OF ACUTE COCAL PHARMACITIS/TOMSILLITIS IN INFANT\$ & CHILD. SUB 9/6/89 ORIG SUB PG 1/319 COCAL PRANCECTIS/TOMSILLITIS IN INFANT\$ & CHILD. SUB PG 1/319 COCAL PRANCECTIS/TOMSILLITIS IN INFANT\$ CHILAD. SUB PG 1/319	E H/1140/	2	TO OF C	REPOR PROX	05USP (100MG/3mL) vs 200mL 16/8/40 #ORIG 5UB PG 1/163
IN FRIGHT OF UNCORP LALE TAWAL TAWAL TAWAL SHELL VS BACTRIM SSUEP 4000G THIRMINING THE STATE OF UNCORP LALE TAWAL OF COURS OF CEPPOR PROX OSUSP 10000G/SHL) & PRINCIPLIAN V POT COURP# (25000G/SHL) IN FRINGT OF ACUTE SINCIPLAN V POT COURP# (25000G/SHL) IN FRINGT OF ACUTE SOCIAL PHARMICITIS/TOWSILLITIS IN INFRM#T#S & CHILD'S SUB 9/6/89 ORIG SUB PG 1/319 SOCIAL PHARMICITIS/TOWSILLITIS IN INFRM#T#S & CHILD'S SUB 9/6/89 ORIG SUB PG 1/319 COUCAL PHARMICITIS/TOWSILLITIS IN INFRM#T C CHILD'S SUB 9/6/89 ORIG SUB PG 1/319 E W/1140/0028 "COMP OF CEPPOD PROX OSUSP (10000G/SHL) & PENICILLIN V POT CSUSP# (2500G/SHL) IN INFRM#T OF ACUTE COCCAL PHARMICITIS/TOWSILLITIS IN INFRM#T S CHILD'S SUB 9/6/89 ORIG SUB PG 1/319 E W/1140/0028 "COMP OF CEPPOD PROX OSUSP (10000G/SHL) & PENICILLIN V POT CSUSP# (2500G/SHL) IN INFRM#T OF ACUTE COCCAL PHARMICITIS/TOWSILL IN INFAMTS & CHILD'S SUB 9/6/89 ORIG SUB PG 1/319 COCCAL PHARMICITIS/TOWSILL IN INFAMTS & CHILD'S SUB 9/6/89 ORIG SUB PG 1/319 COCCAL PHARMICITIS/TOWSILL IN INFAMTS & CHILD'S SUB PG 1/319	IS MEDIA E M/1140/	0020 "CO		EFPOD PROX	OSUSP 100MG/5ML VS BACTRUM OSUSP 40MS 114 SUB PG 1/266
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STRING TOWNSTRIPLITIS IN THE PARTES & CHILDRAN SUB 3/0,107 PCT CSUSP# (250MG/5ML) IN TRIMET DE ACUTE COMP OF CEFPOD PROX CSUSP (100MG/5ML) & PENICILLIN V POT CSUSP# (250MG/5ML) IN IRTHET OF ACUTE COMP OF CEFPOD PROX CSUSP (100MG/5ML) & DENICILLIN V POT CSUSP# (250MG/5ML) IN IRTHET OF ACUTE COMP OF CEFPOD PROX CSUSP (100MG/5ML) & DENICILLIN V POT CSUSP# (250MG/5ML) IN IRTHET COMP OF CEFPOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CEFPOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFPOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CEFFOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFPOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CEFFOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFPOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CEFFOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFPOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CEFFOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFFOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CEFFOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFFOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CEFFOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFFOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CEFFOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFFOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CEFFOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFFOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CERFOD IN PEDIATRIC PTS FLANING ADMIN OF #CEFFOD PROXETIL FOR ORAL SUSP# PRARMANCOMINETICS OF CERFOD FOR PEDIATRIC PTS FLANING ADMIN OF #CEFFOD PROXETIL FOR PEDIATRIC PTS FLANING PEDIATRIC PTS FLANING ADMIN OF #CEFFOD PROXETIL PTS FLANING PEDI	IN TRIM		Character URU	E o	INFECTIS IN INCIDENCE PRINCILLIN V POF OSUSP# (250MG/5ML) I OSUSP (100MG/5ML) & PRINCILLIN V POF OSUSP# (250MG/5ML)
FROM COURTES CRILLO SUB 9/6/89 ORIG SUB PG 1/319 PROM COURTES CRILLO E PENUCILLIN V FOT COURTE [250MG/5ML) IN THIMBT OF ACUTE PROX COURTE (250MG/5ML) E PENUCILLIN V FOT COURTE [250MG/5ML) IN THIMBT OF ACUTE (250MG/5ML) IN THIMBT OF THE SUB PG 1/319 NES E CRILLED SUB 9/6/89 ORIG SUB PG 1/319 S OF CRITCED IN PEDIATRIC PTS FLAMING ADMIN OF #CTFPOD PROXBILL FOR ORAL SUSP.	COCCAL PI		S/TONS		CHENNIAS & CHILDRAN SUB 5/0/85 CALC CSUSP# (250MG/5ML)
PROX OSUSP (100MG/SML) & PERULIMATE 1/319 TES & CHILLED SUB 9/6/89 ORIG SUB PG 1/319 S OF CRIPPOD IN PEDIATRIC PTS FILMING ADMIN OF ECEPDOD PROXBILL FOR ORAL SUSP.	E N/1140	/002B CX) 40 OF (SIFFOD PROX	INFARETS & CRILLO" SUB 9/6/89 ORIG SUB PG 1/319
/TOBSILL IN INTANIS & CHILLY OF SELECTIVE ADMIN OF SCREEDS FROXBILL FOR SELECTIVE ADMIN OF SCREENS FROXBILL FROX	2 N/1140	70028 'C	MP OF (2	OSUSP (100MG/SML) & PENLCILLING V FOR
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CLINICAL DATA SYSTEM LUCI 2.40 LISTING FOR MONDAY, DECEMBER 7, 1992 AT 15:44:39

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CONTRACT				TRANSPORTED ON THE TRANSPORTED TO THE TRANSPORTED T	TOTAL OSUSP (4046 TR\$THE)
SEE M/1140/0020 "COMP	DO20 "CO	Y TRACT	EFFOD PROX	OF CEFPOD PROX GSUSP (100MS/JML) VS BWLLACK BY TABLE CHILDS & CHILDS & SUB 9/6/89 PGS 1/266 TRACT INTERCTS IN INVAMINE (100MS/JML) WE MICHAELT OSCING (250)	by sub 9/6/89 PCS 1/266 ye sub 9/6/80 PCS 1/266
SEE W/1140/0013			CEPPOD PROX	SUB 9/6/849 PG 1/163 ORIG 8UB	ONIG SUB
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PHARMCITIS/TOWNSLILLITS IN INFANCE & CALLED - SUB 2/409 CRIC SUB PC 1/319

PERMICITIS/TOWNSLILLITS IN INFANCE CRICAD PROX OSUSP (1006/94L) & PENICILLIN W POT OSUSP (2508G/54L) IN TRIMIT OF ACUTE STREP

PERMICITIS/TOWNSLILLITS IN INFANTS & CALLED - SUB 9/6/89 ORIG SUB PC 1/310

TO PHARMCITIS/TOWNSLILLITS IN INFANTS & CALLED - SUB 9/6/89 ORIG SUB PC 1/310

TO PHARMCITIS/TOWNSLILLITS IN INFANTS & CALLED - SUB 9/6/89 ORIG SUB PC 1/310

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THARMCITIS/TOWNSLILLITS IN INFANTS & CALLED - SUB 9/6/89 ORIG SUB PC 1/306

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THARMCITIS/TOWNSLILLITS IN INVANTS/CHILLD - SUB 9/6/89 ORIG SUB PC 1/306

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THARMCITIS/TOWNSLILLITS IN INVANTS/CHILLD - SUB 9/6/89 ORIG SUB PC 1/310

THARMCITIS/TOWNSLILLITS IN INVANTS/CHILLD - SUB 9/6/89 ORIG SUB PC 1/310 HT OF ACUTE STREP COTE SUPPORATIVE 158 159 161 161 162 164 166 161 154 155 156 156

CLINICAL DATA SYSTEN LUCI 2.40 LISTING FOR HONDAY, DECEMBER 7, 1992 AT 15:44:39

4					-						+	EPHICTILIN V POT OSUSP (250MG/5ML) IN TREMOT OF ACUTE STREP B PG 1/31D L) VS BACTELH ORAL SUSP # (40MG TRIMETHOPRINE 200MG SULFAMETHOX LL) VS BACTELH ORAL SUSP # (40MG TRIMETHOPRINE 200MG SULFAMETHOX LL) VS BACTELH OSUSP # (40MG TRIMETHORALSOLE & 200MG SULFAMETHOX L) VS ACTILLY V POT OSUSP # (250MG/5ML) IN TRIMET OF ACUTE STR AND PERICILLIN V POT OSUSP # (250MG/5ML) IN TRIMET OF ACUTE STR NUL VS BACTELH OSUSP (40MG TRETMETHORETHIC 200MG SULFAMETHOXAZOLE/5M VS BACTELH OSUSP (40MG TRETMETHORETHIC & 200MGS V TRIMETHOPPHIN/SOLLAMETHORETHIC OSUSP (40MG TRETMETHORETHIC & 200MGS V TRIMETHOPPHIN/SOLLAMETHORETHIC OSUSP (40MG TRETMETHORETHIC & 200MGS V TRIMETHORETHIC OSUSP (40MG TRETMETHORETHIC & 200MGS V TRIMETHORETH OSUSP (40MG TRETMETHORETHIC & 200MGS V TRIMETHORETHIC OSUSP (40MG TRETMETHORETHIC & 200MGS V TRIMETHORETHIC OSUSP (40MG TRETMETHORETHIC & 200MGS V TRIMES ASSAN) " CS ANGOR #11/20/89 FOR COMPERTE COPY OF TRIP SEB IT (AMES ASSAN) " CS ANGOR #11/20/89 FOR COMPERTE COPY OF TRIP SEB T (AMES ASSAN) " CS ANGOR #11/20/89 FOR COMPERTE COPY OF TRIP STR VS AUGMRNTIN OSUSP (250MGF/5ML) IN TRIMET OF ACUTE SUPP OFFITIS
RPAGE		·	را م	••	- 83 -	-l	*		82	- 8 2	1	THE WILL40/0027 "COME OF CHEPOD PROX SOSUP (100MC/SML) & PENICHLIN W POT COURP (250MG/SML) IN THE MAINS (100MC/SML) WE BELLED WILLSON ORDER (1250MG/SML) WE MAINS (100MC/SML) WE WENTER THE STANDARD (100MC/SML) WE MAINS (100MC/SML) WE WENTER (100MC/SML) WE MAINS (100MC/SML) WE WANTS (100MC/SML) WE WANTS (100MC/SML) WE WANTS (100MC/SML) WE MAINS (100MC/SML) WE MAINS (100MC/SML) WE WANTS
PAT TRHUM					1224/90/009				7228/89/019	1228/89/019		127 "COMP OF CHIPDO PROX SOSUR (100MG/SML) & PERICILLIN V. L. IN INFANTS & CHILD" SUR 9/16/89 ORIG SUB PG 1/31D 2. IN INFANTS & CHILD" SUR 9/16/89 ORIG SUB PG 1/31D 2. "COMP OF CHEPOD PROX (100MG/SML) VS BACTRIN V. COMP OF CHEPOD PROX (100MG/SML) VS ACTRIN V. COMP OF CHEPOD PROX (200F 100MG/SML) NO PERICILLIN V. COMP OF CHEPOD PROX OSUSP (100MG/SML) NO PERICILLIN V. COMP OF CHEPOD PROX OSUSP (100MG/SML) VS BACTRIN COMPONENT I FERTILLITY AND CHERAL REPRODUCTIVE PERICEMANCY SEGRETY I FERTILLITY AND CHERAL REPRODUCTIVE PERICEMANCY COMPONENT IN TRACT INFANTS (100MG/SML) VS BACTRIM OF UNCOM UNIX TRACT INFECTS IN INFANTS (CHILD" SUB 9/6 OF UNCOM UNIX TRACT INFECTS IN INFANTS (CHILD" SUB 9/6 OF UNCOMP UNIX TRACT INFECTS IN INFANTS (CHILD" SUB 9/6 OF UNCOMP UNIX TRACT INFECTS IN INFANTS (CHILD" SUB 9/6 OF UNCOMP UNIX TRACT INFECT IN INFANTS (CHILD" SUB 9/6 OF UNCOMP UNIX TRACT INFECT IN INFANTS (CHILD" SUB 9/6 OF UNCOMP UNIX TRACT INFECT IN INFANTS (CHILD" SUB 9/6 OF UNCOMP UNIX TRACT INFECT IN INFANTS (CHILD" SUB 9/6 OF UNCOMP UNIX TRACT IN UNIX TRACT INFANTS (CHILD" SUB 9/6 OF UNCOMP UNIX TRACT IN UNIX TRA
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9/25/90# **COMPARISON OF DEXEP PROMETLY POWDRR POR ORAL SUSPENSION VS CENTINE POWDER # 9/25/90# **COMPARISON OF DEXEP PROMETLY POWDRR ORAL SUSPENSION VS CENTINE POWDER POR ORAL SUSPENSION IN THE TREM** **COMPARISON OF DEXEP PROMETLY POWDRR POR ORAL SUSPENSION VS CENTINE POWDER POR ORAL SUSPENSION IN THE TREM** **COMPARISON OF DEXEP PROMETLY POWDRR POR ORAL SUSPENSION VS CENTINE POWDER POR ORAL SUSPENSION IN THE TREM** **COMPARISON OF DOKEP PROMETLY POWDER POR ORAL SUSPENSION VS CENTINE POWDER POR ORAL SUSPENSION IN THE TREM** **COMPARISON OF DOKEP PROMETLY POWDER POR ORAL SUSPENSION VS CENTINE POWDER POR ORAL SUSPENSION IN THE TREM** **COMPARISON OF DOKEP PROMETLY POWDER POR PRANTNCITIS** **COMPARISON OF DOKEP PROMETLY POWDER POR DEAL SUSPENSION VS CENTINE POWDER POR ORAL SUSPENSION IN THE TREM** **COMPARISON OF DOKEP PROMETLY POWDER POR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEP VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS** **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS* **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS* **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS* **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS* **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS* **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER V FOR PHARMOSTIS* **DOKEP PROMETLY GRAL SUSPENSION DOKEF VS PER	COMERATION OF DOKEP PROMETLY PORDER FOR ORAL SUBPRISION VS CEVIDE POWDER \$ 9475/904 COMERATION OF DEXEP PROMETLY POWDER POR ORAL SUBPRISION VS CEVIDE POWDER \$ 975/904 COMERATION OF DEXEP PROMETLY POWDER FOR ORAL SUBPRISION VS CEVIDE POWDER \$ 975/904 COMERATION OF DEXEP PROMETLY POWDER FOR ORAL SUBPRISION VS CEVIDE POWDER \$ 975/904 COMERATION OF DEXEP PROMETLY POWDER FOR ORAL SUBPRISION VS CEVIDER POWDER \$ 975/904 COMERATION OF DEXEP PROMETLY POWDER FOR ORAL SUBPRISION VS CEVIDER POWDER \$ 975/904 COMERATION OF DEXEP PROMETLY POWDER FOR ORAL SUBPRISION VS CEVIDER POWDER FOR CRAL SUBPRISION IN THE TREAT PROMETRY POWDER FOR ORAL SUBPRISION IN THE TREAT PROMETRY PROMETRY FOR ORAL SUBPRISION VS CEVIDER POWDER FOR CRAL SUBPRISION IN THE TREAT PROMETRY FOR DEATH OF DEATH PROMETRY FOR DEATH POWDER FOR PHARMAGITIS * 10/19/894 † COMERATIVE OFFICE SUBPRISION DOXEP VS PRIN V FOR PHARMAGITIS * 10/19/894 † FOWER PROMETLY GRAL SUBPRISION DOXEP VS PRIN V FOR PHARMAGITIS * 10/19/894 † FOWER PROMETLY GRAL SUBPRISION DOXEP VS PRIN V FOR PHARMAGITIS * 10/19/894 † FOWER PROMETLY GRAL SUBPRISION DOXEP VS PRIN V FOR PHARMAGITIS * 10/19/894 † FOWER PROMETLY GRAL SUBPRISION DOXEP VS PRIN VERTICALLY V POTASSIUM FORL SUBPRISION IN THE PROMETRY OR DAXE VS PRIN VERTICALLY V POTASSIUM FORL SUBPRISION DOXEP VS PRIN VERTICALLY V POTASSIUM FORL SUBPRISION DOXEP VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY GRAL DOXEP VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY GRAL SUBPRISION DOXEP VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY OF THE PROMETRY OR DAXE VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY GRAL DOXEP VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY OR DAXE VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY OR DAXE VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY OR DAXE VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY OR DAXE VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY OR DAXE VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY OF THE PROMETRY OR DAXE VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY OR DAXE VS PRINKVETTIS * 10/19/894 † FOWER PROMETRY OF TH	FARI	8 % 8 %	CDOX INE		W. 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ACUTE SUPPURATIVE OTITIS MEDIA IN INFARTY SAND CHILDREN" 9/25/90 *COMPARISON OF DOME PROMETIL POMDER FOR GRAL SUSPENSION VS CRETAINER POMDER FOOR CRAL SUSPENSION IN THE TRIA. "COMPARISON OF DOME PROMETIL PUMDER FOR ORAL SUSPENSION WS CRETAINER POMDER FOOR CRAL SUSPENSION IN THE TRIA. "COMPARISON OF DOME PROMETIL CRAL SUSPENSION DOME VS PRN V FOR PHARMWRITIS" 10/19/89# # *DOME PROMETIL CRAL SUSPENSION DOME VS PRN V FOR PHARMWRITIS" 10/19/89# # *DOME PROMETIL CRAL SUSPENSION DOME VS PRN V FOR PHARMWRITIS" 10/19/89# # *DOME PROMETIL CRAL SUSPENSION DOME VS PRN V FOR PHARMWRITIS" 10/19/89# # *DOME PROMETIL CRAL SUSPENSION DOME VS PRN V FOR PHARMWRITIS" 10/19/89# # *DOME PROMETIL CRAL SUSPENSION DOME VS PRN V FOR PHARMWRITIS" 10/19/89# # *COMPARISON OF GNAL DOME PROMETIL ORAL SUSPENSION AND PERICTLIN V POTASSIUM FORAL SUSPENSION IN THE TREATM COMPARISON OF GNAL SUSPENSION PROMETICAL ORAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION NAD PRINCILLIN V POTASSIUM GRAL SUSPENSION IN THE "COMPARISON OF GNAL SUSPENSION GNAL SUSPENSI	ACUTE SUPPURATIVE OTITIS MEDIA IN INFANTS AND CHILDREN" 9/25/90 *COMPARISON OF DOKEP PROXETIL POMDER FOR GRAL SUSPENSION WS CRFIXING POMDER FOOR CRAL SUSPENSION IN THE TRIA. "COMPARISON OF DOKEP PROXETIL PURDER FOR GRAL SUSPENSION IN THE TRIA. "COMPARISON OF DOKEP PROXETIL GRAL SUSPENSION DOKEP WE PROXETIL GRAL SUSPENSION AND PRINCILLIN V POTA\$SIUM ORAL SUSPENSION IN THE "COMPARISON OF GRAL GEPOMOSTHE PROXETIL ORAL SUSPENSION AND PRINCILLIN V POTA\$SIUM ORAL SUSPENSION IN THE "COMPARISON OF GRAL GEPOMOSTHE PROXETIL ORAL SUSPENSION AND PRINCILLIN V POTA\$SIUM ORAL SUSPENSION IN THE "COMPARISON OF GRAL GEPOMOSTHE PROXETIL ORAL SUSPENSION AND PRINCILLIN V POTA\$SIUM ORAL SUSPENSION IN THE "COMPARISON OF GRAL GEPOMOSTHE PROXETIL ORAL SUSPENSION AND PRINCILLIN V POTA\$SIUM ORAL SUSPENSION OF GRAL GEPOMOSTHE STREPTOCOCCAL PHARVAGITIS ULE TO STREPTOCOCCUS PYGGENES"	ACUTE SUPPURATIVE OTITIS HEDIA IN IMPARIS AND CHILDREN" 9/25/90 **COMPARISON OF DOKEP PROMETIL POWDER FOR ORAL SUSPENSION VS CRFIXING POWDER FOOR ORAL SUSPENSION IN THE TRLA. **COMPARISON OF DOKEP PROMETIL POWDER FOR ORAL SUSPENSION VS CRFIXING POWDER FOOR ORAL SUSPENSION IN THE TRLA. **COMPARISON OF DOKEP PROMETIL POWDER VS PEN V FOR PHARYNGITIS" 10/19/89# # **DOKEP PROMETIL GRAL SUSPENSION DOKEF VS PEN V FOR PHARYNGITIS" 10/19/89# # **DOKEP PROMETIL GRAL SUSPENSION DOKEF VS PEN V FOR PHARYNGITIS" 10/19/89# # **DOKEP PROMETIL GRAL SUSPENSION DOKEF VS PEN V FOR PHARYNGITIS" 10/19/89# # **DOKEP PROMETIL GRAL SUSPENSION DOKEF VS PEN V FOR PHARYNGITIS" 10/19/89# # **DOKEP PROMETIL GRAL SUSPENSION DOKEF VS PEN V FOR PHARYNGITIS" 10/19/89# # **DOKEP PROMETIL GRAL SUSPENSION DOKEF VS PEN V FOR PHARYNGITIS" 10/19/89# # **DOKEP PROMETIL GRAL SUSPENSION DOKEF VS PEN V FOR PHARYNGITIS" 10/19/89# # **DOKEP PROMETIL GRAL SUSPENSION DOKEF VS PEN V FOR PHARYNGITIS" 10/19/89# # **COMPARISON OF ORAL DOKEF PROMETIL ORAL SUSPENSION AND PRINCILLIN V POTA\$SIUM ORAL SUSPENSION IN THE "COMPARISON OF ORAL CEPONOLIME PROMETIL ORAL SUSPENSION ENDINE TO STREPTOCOCCUS PYOGENES" **COMPARISON OF ORAL CEPONOLIME PROMETIL ORAL SUSPENSION AND PRINCILLIN V POTA\$SIUM ORAL SUSPENSION IN THE "COMPARISON OF ORAL CEPONOLIME PROMETIL ORAL SUSPENSION ENDINE TO STREPTOCOCCUS PYOGENES"	COMPARIS	DOOR BOTH	EP PROXE		9	STAR MAL BOOK CONTRACTOR OF THE STAR STAR STAR STAR STAR STAR STAR STAR
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COMPARISON OF CHILLS HEDIA IN INTRAFFS AND CHILDREN 9/25/90 **PACTE SUPPERATIVE CHILLS HEDIA IN INTRAFFS AND CHILDREN** 9/25/90 **POCKET PROCETIL GRAL SUSPENSION DOINE VS PEN V FOR PHARYNGITIS** 10/19/89# # **DOKET PROCETIL GRAL SUSPENSION DOINE VS PEN V FOR PHARYNGITIS** 10/19/89# # **DOKET PROCETIL GRAL SUSPENSION DOINE VS PEN V FOR PHARYNGITIS** 10/19/89# # **DOKET PROCETIL GRAL SUSPENSION DOINE VS PEN V FOR PHARYNGITIS** 10/19/89# # **COMPARISON OF ORAL DOXET PROCETIL GRAL SUSPENSION AND PERSICIALIN V POTASSIUM ORAL SUSPENSION IN THE ** **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS** # **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS** # **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS** # **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS** # **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OR ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OR ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS* ** **COMPARISON OF ORAL SUSPENSION DOXET VS PEN V FOR PHARYNGITIS OF VS PEN V FOR PHARYNGIT	**COMPARISON OF ORAL SUSPENSION DOXEE VS PRN V POR PHARYNGITIS*** \$\frac{1}{2} = \text{ACTE SUSPENSION DOXEE VS PRN V POR PHARYNGITIS** \$\frac{1}{2} = \text{ACTE SUSPENSION DOXEE VS PRN V POR PHARYNGITIS** \$\frac{1}{2} = \text{ACTE SUSPENSION DOXEE VS PRN V POR PHARYNGITIS** \$\frac{1}{2} = \text{ACTE PROCETIL GRAL SUSPENSION DOXEE VS PRN V POR PHARYNGITIS** \$\frac{1}{2} = \text{ACTE PROCETIL GRAL SUSPENSION DOXEE VS PRN V POR PHARYNGITIS** \$\frac{1}{2} = \text{ACTE PROCETIL GRAL SUSPENSION DOXEE VS PRN V POR PHARYNGITIS** \$\frac{1}{2} = \text{ACTE STREP PHARTNGITIS TONSILLITIS IN INF \$\frac{1}{2} = \text{ACTE PROCETIL ORAL SUSPENSION DOXEE VS PRN V POR PHARYNGITIS** \$\frac{1}{2} = \text{ACTE PROCETIL ORAL SUSPENSION DOXEE VS PRN V POR PHARYNGITIS** \$\frac{1}{2} = \text{ACTE STREP PHARTNGITIS TONSILLITIS IN INF \$\frac{1}{2} = ACTE STREPTOCOCCAL PHARYNGITIS TONSILLITIS UNE TO STREPTOCOCCUS PYGGENES**	POCKE PROCETIL GRAL SUSPENSION DOINE VS PRN V FOR PHARYNGITIS" 10/19/89# # DOKEP PROCETIL GRAL SUSPENSION DOINE VS PRN V FOR PHARYNGITIS" 10/19/89# # DOKEP PROCETIL GRAL SUSPENSION DOINE VS PRN V FOR PHARYNGITIS" 10/19/89# # DOKEP PROCETIL GRAL SUSPENSION DOINE VS PRN V FOR PHARYNGITIS" 10/19/89# # DOKEP PROCETIL GRAL SUSPENSION DOINE VS PRN V FOR PHARYNGITIS" 10/19/89# # DOKEP PROCETIL GRAL SUSPENSION DOINE VS PRN V FOR PHARYNGITIS" 10/19/89# # COMPARISON OF ORAL DOKEP PROCETIL GRAL SUSPENSION AND PERICILLIN V POTASSIUM FORAL SUSPENSION IN THE COMPARISON OF ORAL SUSPENSION DOKEF VS PRN V FOR PHARYNGITIS" # COMPARISON OF ORAL CEPODOTHE PROXETIL ORAL SUSPENSION AND PRNICILLIN V POTASSIUM ORAL SUSPENSION IN THE "COMPARISON OF ORAL CEPODOTHE PROXETIL ORAL SUSPENSION AND PRNICILLIN V POTASSIUM ORAL SUSPENSION IN THE "COMPARISON OF ORAL CEPODOTHE PROXETIL ORAL SUSPENSION AND PRNICILLIN V POTASSIUM ORAL SUSPENSION IN THE "COMPARISON OF ORAL CEPODOTHE PROXETIL ORAL SUSPENSION AND PRNICILLIN V POTASSIUM ORAL SUSPENSION IN THE "COMPARISON OF ORAL CEPODOTHE PROXETIL ORAL SUSPENSION AND PRNICILLIN V POTASSIUM ORAL SUSPENSION IN THE "COMPARISON OF ORAL CEPODOTHE PROXETIL ORAL SUSPENSION AND PRNICILLIN V POTASSIUM ORAL SUSPENSION IN THE "COMPARISON OF ORAL CEPODOTHE PROXETIL ORAL SUSPENSION AND PRNICILLIN UP STREPTOCOCCAL PHARYNGITIS/TONS FILLITIS OUT TO STREPTOCOCCUS PYGGENES"	P ACUTE S	OPPOKATIVA OF OF POS	MUDDE A	ETTY POPOER		PONDER FORM COMPANIES
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DOXEFTH Branules

- RED 1-9-90 Amendment 004 Submitted Protocol P/1140/0032 Part 6 for Jacobs
- RED 1-30-90 Amendment 005
 Submitted Part 6 Protocol M/1140/0013 Cornay,
 M1140/0020 Foulds, Maderazo, Paster, Wiederhold,
 M/1140/0027 Chiulli, Hedrick, Kline, Mendelson, Wiederhold,
 M/1140/0028 Foulds, Frenkel, Revisions M/1140/0020 Bocchini,
 M/1140/0028 Foulds, Frenkel, Revisions M/1140/0020 Bocchini,
 Gooch, Hooper, McCarty and listed subinvestigators
- RED 3-3-90 Smrnfmrny 006
 Request a meeting to demonstrate what we are now capable of providing electronically
- JRB 2-20-90 Amendment 007 Part 6. Protocol M/1140/0020 Goudarz1. Olk. M1140/0028 Olson
- JRB 3-9-90 Amendment 008
 Part 6 M/1140/0020 Cohen, Nahata, ST111, Revisions
 M1140/0020 Rodriguez and new subinvestors. TRs
 7228/89/019 Ames Assay. TR 7224/90/009 Oral Rat
- RML 3-20-90 Amendment 009
 Request a meeting to demonstrate CANDAR for NDA
- JRB 4-3-90 Amendment 010
 Part 6 M/1140/0013 Feinberg, M/1140/0020 Fainberg, Straub and subinvestigators
- RWL 4-5-90 Amendment 011 Confirming meeting for 4-19-90 at 10:00 a.m. per telephone conversations
- JAE 4-20-90 Request a "PRE_NDA meeting" to discuss scope of NDA
- RWL 5-16-90 Amendment 14
 Submitted prototypes of data displays for screens re
 CANDA per request
- JAE 5-23-90 Af15
 Submitted additional info on the Statistical Analysis
 plans in preparation for Pre NDA filing meeting on 6-18-90
- JAE 5-30-90 Af16
 Submitted Safety Report re a nine month old female who received four times dosage with no serious adverse effects
- JAE 7-10-90 A#18
 Submitted Safety Report re event which was serious and unexpected from Japan
- JAE 7-11-90 Amendment #19
 Submitted Part 6 N/1140/0020 Smith

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DOXEP Flavored Granules

- RML 7-18-90
 Request comments re M/1140/0043, 0044 & 0045 prior to formal submission from Dr. Susan Alpert per request
- CPE 7-25-90 Amendment #020
 Submitted Safety Reports which were serious and unexpected from Japan where marketed :
- JAE 8-3-90 Amendment #021
 Submitted modified tables for review and a brief aummary of telephone conversation of 7-17-90
- JAE 8-7-90 Submitted several journal articles we failed to include with our 7-18-90 letter
- JAE 4-23-90 A#012 Submitted Part 6/1-16 Protocol P1140/0035, Bluestone 6/17-20 & Labeling Page 7/1
- JAE 4-30-90 Af013
 Submitted Part 6/1-31Protocol M1140/0020, McLinn, Rettig,
 Tyler & co/inv., Part 7/1 Labeling
- JAE 5-31-90 A#017 Submitted Part 6/1-14 Protocol M1140/0020, Drehobl, Puopolo, Goldblatt, co/invs. & Part 7/1 Labeling
- JAE 9-25-90 A#22
 Submitted Part 6/1-73, Protocol Mil40/0043, Hedrick, McLinn, Wiederhold, Protocol Pil40/0038 Hughes & co/invs, Part 7 Labeling
- JAE 10-31-90 A#23
 Submitted Part 6 1-48, Protocol N1140/0020 Cohen co/inv., Protocol N1140/0043 Dajani, Neiderman, Mendelman, Shelton, Shirin, a Change in Protocol M1140/0038 Page 49
- JAE 11-5-90
 Please submit our tradename to FDA's Labeling and Nomenclature
 Committee for an assessment of our tradename
 - JAE 12-17-90 A#24 Submitted Annual Report
 - JAE 12-18-90 A#25 Submitted Protocol M1140/0043 Bowerl-4 & subs, Simoes 5-12, Bluestone 12-18. list of subs

VANTIN @ Flavored Granules IND 33,641 (name changed from Dozef 4-27-92)

- 1-11-91 Comments re 11-6-90 meeting re proposed CANDA Submission date for the NDAs is 3-29-91
- 3-11-91 A#026 Submitted Part 6/1-5 Felder added sub for Bluestone P/1140/0036, 6/6-53 TR 9155/90/018, 6/54-100 TR 9155/90/021
- 5-2-91 A#27 to add Feinberg to Protocol M1140/0043 Part 6/1-4
- 5-7-91 A#001 Addendum includes Amendment #1 for Dennis L. Swartout for Protocol M1140/0028 which was inadvertently omitted from A#001
- 5-28-91 Declare the trade name DOXEF to be unacceptable because of safety and another name should be proposed
- 6-21-91 A#28 Submitted Howie to Protocol M/1140/0048 1-18 & subs and Chanin 14-21 same protocol
- 8-30-91 A#029 Submitted Page 1-15 Protocol P/1140/0058 Peters 16-18, Labeling 19-20
- 10-16-91 A#030 Submitted Pages 2-37 Protocol M/1140/0054 Gooch & subs 38-77, Labeling 78-79
- 11-12-91 A#31 Submitted Part 7/1-44 Chemistry/Mfg/Control
- 11-18-91 A#32 Submitted New investigator Stephen Aronaff & co's 1-14 Protocol M/1140/0054, 15-39 Blumer & co
- 12-11-91 A#83 Submitted New Protocol M/1140/0059, Investigarot Adna S. Dajani and Sub/Inv Mirta Soler, Jennie Andersen, Chandra Edwin, Protocol change (amendment 1) can be found on page 38a of this submission, part 7 labeling is provided for protocol M/1140/0054 and also applies to the protocol M/1140/0059
- 12-13-91 A#33 Submitted new protocol P/1140/0039, pages 1 14, investigator Albert
 J. Diets
- 1-3-92 A#34 (corrected amendment No.) Submitted new protocol P/1140/0038, pages 1 14, investigator Albert J. Diets
- 1-10-92 A#35 Protocol amendment, new investigators M/1140/0054 multicenter study, Investigator Richard F. Jacobs, Sub/Inv Gordon E. Schutze, Joseph Elser, Toni Darville, Nancy Tucker, Investigator Michael E. Pichichero, and Sub/Inv Frank A. Disney, John L. Green, Anne B. Francis, Steven M. Rarsocci, Marie Lynd, Gordon C. Wood
- 1-17-92 A#36 Submitted Safety Report Medical Event: Pancolitis

1-21-92 A#87 Submitted protocol amendment, new investigator M/1140/0054, William Rodriguez, subinvestigators, Waheed N. Khan, Om P. Chhabra, Tahir Bait, Arthur Guarinallo, Alan W. Smith. Protocol Change P/1140/0039 (amendment 1) is necessary for protocol instructions regarding constitution of the investigational lot (lot 25,255) made in Belgium to be consistent with the final labeling of the product. Part 7 - Labeling - pages 22-24

2-21-92 A#88 Submitted Annual Report - time period from July 7, 1990 - July 6, 1991

5-14-92 A#39 - Information amendment to include the following clinical technical reports: TR 9155/90/33, TR 9155/90/001, TR 9155/91/006, TR 9155/90/37

7-24-92 A#40 - Submitted Safety Report

APPENDIX C-4

Summary of Correspondence During NDA for VANTIN Granules (Formerly called DOXEF Granules)

Cespodoxime Proxettl Flavored Granules (DOXEF®) NDA 50-675 (Name changed to TUCEFTM 9-91) (Name changed to VANTING 4-27-92)

8.29.91 Submitted original NDA

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3-29-91 FDA acknowledged receipt

4-11-91 Filing date will be 5-29-91

8-13-91 Received fax of deficiencies in the CMC sections

8-15-91 Received a copy of the Microbiology Section Review

3-6--92 Extension of FDA review time to 6/29/92

8-7-92 NDA 50-674 & 50-675 are approved effective as of the date of this letter

4-16-91 Notifies FDA that we will deliver equipment to them that will be used to review the Chemistry-Manufacturing-Control sections of the NDA (optical drive, etc.) un 4-18-91

5-14-91 Providing samples for assay methods validation as requested by FDA

5-20-91 Submitted corrected pages for original NDA 5.21.91 Ack'd receipt

5-29-91 Submitted components and values of the workstation delivered to Dr. Susan Alpert on 5-2-91

6-19-91 Submitted revised pages for Volume 1.1 index 6.20.91 Ack'd receipt

7-11-91 Submitted TUC personnel and issues for discussion for 7-17-91 meeting 7.11.91 Ack'd receipt

7-26-91 Submitted 5 Protocols prior to beginning testing program per meeting of 7-17-91

8-29-91 FDA will accept release of bulk on basis of Sankyo assay. TUC must perform all tests on first 8 lots and every 10th lot thereafter

9-13-91 A#1 Submitting a safety update (1st submission with new name TUCBF116) 5 volumes

9-16-91 Mary still has this submission 10-3-91 Consider a major amondment and have determined t hat 180 additional days will be required for its review 3-14-92 is new date

10-4-91 Providing with two copies of domestic pivotal study protocols and their corresponding list of investigators per request

11-11-91 Submitted Environmental Assessment which Sankyo prepared for inclusion in its DMF

12-13-91 - The status of Case 903 and Case 913, Protocol M/1140/0013 has been revised due to new information. The organisms from both individuals were susceptible. Both cases received cafpodoxime and were considered bacteriologic cure.

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- 12-19-91 Submitted revised Microbiology Section in the package insert as suggested in FDA fax dated 8/14/91 except for retaining "(including penicillinase- and non-penicillinase producing strains)"
- 1-15-92 A#2 Submitted Safety Report, safety info is summarized for the reporting period of Oct 1, 1990 (NDA cut off date) to July 7, 1991)
 1-15-92 Acknowledged Receipt
- 1-30-92 Submitted draft CFR monographs
- 2-10-92 Per telephone last week we sent the TasoHaas column (Number STIM4987) for validation of T/A 1675
- 2-12-92 Submitted A#3 Environmental Assessment 2-18-92 Acknowledged receipt
- 2-18-92 Submitted the following corrections that have been made to TR 9155-90-018 page 2 Conclusions: (moved from first to third bullet) and page 45 Conclusions (moved from first to third bullet)
- 3-5-92 Submitted Technical Report #7215/92/005 entitled "Bioequivalence Study of Clinical Lot and Production Lot of Cespodoxime Proxettl Flavored Granules (Protocol P/1140/0039)
- 3-6-92 Provided responses to the deficiencies in the Control/Manufacturing section of the NDA
- 8-25-92 -Addendum to A#3, per request of Dr. Phillip Vincent, all raw data is submitted in 7 volumes. Only one archival copy will be submitted to each NDA per telephone conversation with Ms Peter Dionne
- 8-31-92. We are revising the Microbiology section of the cefpodoxime proxetil tablets and oral suspension insert to include the following statement in the second sentence of the first paragraph: "Cefpodoxime is highly stable in the presence of beta-lactamase ensymes. As a result, many organisms resistant to penicillins and some cephalosparins, due to the presence of beta-lactamases, may be susceptible to cefpodoxime.
- 4-8-92 Submitted CMC section of Item 3 "Chemistry-Manufacturing-Cjontrol"
- 4-28-92 CANDA equipment has been removed from the office of Mr. Peter Dionne, HFD-520

4-30-92 - A#4 - Minor revisions should be made in Item 8, production lot size, adjustment in the excipient ranges for the amount of opadry applied, change in order of mixing binder solution components, identification debossed on tablet and removal of in-process control test for film coated tablet moisture

4-80-92 - FDA Acknowledged receipt

5-28-92 A#5 - Submitted updated stability data for VANTIN Oral Suspension to request an 18 month expiration dating stored at room temperature. A meeting has been scheduled for June 4 with Peter Dionne, PhD and Mr. Carmen DeBellas to discuss this data.

6-2-92 . We are in receipt of the FDA May 7, 1992 review of the Environmental Assessments for VANTING Tablets, NDA 50-674 and VANTING for Oral Suspension NDA 50-678 and have listed the comments from the FDA, and our responses. This information responds to all deficiencies listed in the May 7 review.

6-9-92 · Provided the following information in response to requests made from June 5, 1992 telephone discussion with Jeff Mehring, Upjohn: 1) Calculations pertaining to environmental concentrations of released substances are shown in Section 8. Thiss includes a calculation for the MEEC. 2) An additional summary table for environmental parameters.

6 15 92 Af6 Submitted information which was presentated at meeting of June 1, 1992 between TUC and the FDA.

6-17-92 - Ack'd receipt

6-15-92 - Submitted revisions in the package insert for VANTIN Tablets and Oral Sluspension as requested by the FDA review dated March 23, 1992.

6-16-92 - Notified FDA that two submissions to the New Drug Applications had misnumbered two amendments: Amendment No. 4 - dated April 30, 1992 - should be Amendment No. 5 and Amendment No. 5 - dated May 28, 1992 - should be Amendment No. 6

6-17-92 - Ack'd receipt

6-16.92 · Submitted changes of Technical Report #89155-90-021 (Protocol M/1140/0027). This report is located in Volumes 8.9 and 8.10 (overall Volumes 1.13 and 1.14) of NDA 50-675.

6-17-92 - Aok'd receipt

6-23-92 · Submitted inserts for distribution in countries other than the United States per FDA request

6-23-92 - Letter to Jerry Abramson, Ph.D, FDA, reference to Item#1, Sankyo has not been assigned a DMF number by FDA

6-30-92 - Submitted a copy of the cespodoxime proxetil Environmental Assesment which may be released under Freedom of Information. This fulfills the commitment made in our letter duted June 2, 1992.

- 7-2-92 Resubmitted a copy of the cofpodoxime proxetil Environmental Assessment which may be released under Freedom of Information. MSDSs in Item 15 have been replaced with itmeized charts
- 7-13-92 A#7 Submitted a third safety update for the period July 8, 1991 to June 1, 1992.
 - 7-13-92 · FDA ack'd receipt
- 7-14-92 Amendment to June 30, 2992 Environmental Assessment. A MEEC for the fifth year of production has been added as you have requested.
- 7-23-92 Resubmitting pages 15 and 16 of the Freedom of Information copy of Upjohn's Environmental Assessment for cespodoxima proxetil.
- 7-24-92 Letter to the FDA granting permission for Dr. Susan Alpert, FDA, to demonstrate our CANDAR system at the Pharmaceutical Manufacturers Association meeting on October 26 and 27, 1992.
- 8-10-92 Pre-launch promotional materials to be used as soon as possible prior to the markett launch of VANTIN® TM Oral Suspension and Tablets which is scheduled for October 1992
- 8-14-92 Per August 7, 1992 approval letter for NDA 50-674 abd 50-675, we are submitting twelve final printed inserts (Code 5R2105/1).
- 8-17-92 Letter to FDA from Kathleen J. Day endosing press kit for VANTIN® Oral Suspension and tablets. A copy of final labeling is also provided.
 - 8-31-92 FDA recommends eliminating use of "extended spectrum" or any comparable claim.
- 8-19-92 Letter to FDA from Kathleen J. Day enclosing core introductory promotional materials for VANTING Oral Suspension and Tablets to be used at market launch in October 1992.
 - 9-17-92 FDA comments and/or recommendations on Primmary Care Introductory Ad and Comprehensive Detailer
- 8-21-92 · Submitted supplement to add statements to the package insert on Clinical Pharmacology "Effects of Food" and Dosage and Administration 8-27-92 · FDA acknowledged receipt
- 9-3-92 Response to questions raised by Dr. Charles Kumkumian, FDA. "Both NF and non-NF Carrageenan gum are listed in the excipients of VANTIN Oral Suspension. Which is used?"
- 9-17-92 Letter to FDA that Sankyo, Tokyo, Japan informed us that Amendment 5 was submitted to their Drug Master File on Augusty 28, 1992.
- 9-29-92 Per FDA request of August 7, 1992 approval letter, we are supplying the FDA with one bottle and carton for VANTIN Tablets 100 mg and VANTIN for Oral Suspension 100 mg/5 ml.

APPENDIX D

Declaration of Attorney

PATENT/Docket No. 4722 EX U.S. Patent 4,486,425 Application for Extension Appendix D-1

APPENDIX D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re

U.S. Patent 4,486,425

Issued

4 December 1984

To

Hideo Nakao, Koichi Fujimoto, Sadao Ishihara, Shinichi Sugawara, Isamu

Igarashi

For

7-[2-(2-Aminothiazol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-Methoxymethyl-3-

Cephem-4-Carboxylates

Commissioner of Patents and Trademarks Box Patent Extension Washington, DC 20231

DECLARATION

Sir:

The undersigned attorney, who has been given Power of Attorney by Sankyo Co. Ltd., which is the Applicant for Extension of Patent Term under 35 USC 156 with regard to U.S. Patent 4,486,425, hereby declares as follows:

- 1. THAT he is a patent attorney authorized to practice before the Patent and Trademark Office and has general authority from the owner to act on behalf of the owner in this patent matter;
- 2. THAT he has reviewed and understands the contents of the application being submitted pursuant to 35 USC 156 and 37 CFR 1.740;
- 3. THAT he believes the patent is subject to extension pursuant to 35 USC 156 and 37 CFR 1.710;
 - 4. THAT he believes an extension of the length claimed is fully justified under 35 USC 156;
- 5. THAT he believes the patent for which the extension is being sought meets the conditions for extension of the term of patent as set forth in 35 USC 156 and 37 CFR 1.720 if the Commissioner

PATENT/Docket No. 4722 EX U.S. Patent 4,486,425 Application for Extension Appendix D-2

agrees with the interpretation of the law that Applicant is requesting in paragraph 5(A) of the application for extension.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made on information and believe are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

7 December 1992 Date

awrence T. Welch

APPENDIX E

Certificate of Correction and Maintenance Fee Receipts

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 4,486,425

: December 4, 1984

INVENTOR(S): Hideo Nakao et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, Left Column, under the heading "U.S. PATENT DOCUMENTS" insert

--4,278,793 7/1981 Durckheimer et al......544/21---

Column 25, line 43: replace "4.20" with --4.10--.

Attesting Officer

Column 33, line 28: replace "CH $_3$ e,uns/CH/ $_2$)" with

--CH₃СН₂)---

Bigned and Bealed this

Twenty-fourth Day of September 1985

DONALD J. QUIGG

Commissioner of Patents



UNITED STATES DEPARTMENT OF COMMERCE Patent and Trademark C Patent and Trademark C

COMMISSIONER OF PATENTS AND TRADEMARKS

PAYOR NUMBER 001933

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WOODWARD, P.C.

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The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY COR-RECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR · 中国1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.8014. WAY IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE ties IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (I). A system of the long of the line of the control

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If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

> ITM ATTY DKT. NUMBER : NRR

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DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231



UNITED STATES DEP/ MENT OF COMMERCE Patent and Trademark O. ...

Address: COMMISSIONER OF PATENTS AND TRADEMARKS

PAYOR NUMBER 001933

FRISHAUF, HOLTZ, GOODMAN & WOODWARD, P.C. 261 MADISON AVENUE NEW YORK NY 10016 RECEIVED

FEB 25 1988

DATE MAILED 02/18/88

FRISHAUF, HOLTZ.

038198

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (i).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

			FEE AMOUNT	SUR Charge	SERIAL Number	PATENT Date	FILE Date	PAY YR		
. 1	4,486,425	170	225		06/304,988	12/04/84	09/23/81	04	NO	PAID
2	4,487,781	170	225		06/410,695	12/11/84	08/23/82	04	NO	PAID
3	4,486,497	170	225		06/395,966	12/04/84	07/07/82	04	NO	PAID
4	4,474,733	170	225		06/350,048	10/02/84	02/18/82	04	NO	PAID
5	4,482,686	173	450		06/538,352	11/13/84	10/03/83	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITH	ATTY DKT
NBR	NUMBER
1	81597
2	80386C
3	82400
Δ	07105

DIRECT THE RESPONSE TOGETHER WITH PART B OF THIS NOTICE, AND ANY QUESTIONS ABOUT ANY NOTICE TO:

COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

APPENDIX F

Declaration of Hiroshi Oda (Original to be Filed upon Receipt) 12月 78 (月) 10:41 サンキョウ(カフェ) トゥキョフェ 03-492-3754

PATENT/Docket No. 4722 EX U.S. Patent 4,486,425 Application for Extension Appendix F-1

APPENDIX P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

in re

U.S. Patent 4,486,425

Issued

4 December 1984

To

Hideo Nakao, Koichi Pujimoto, Sadao Ishihara, Shinichi Sugawara, Isamu

Igarashi

For .

7-[2-(2-Aminothiazol-4-yl)-2-(Syn)-Methoxyiminoacetamido]-3-Methoxymethyl-3-

Cephem-4-Carboxylates

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, DC 20231

DECLARATION OF HIROSHI ODA

Sir:

- I, Hiroshi Oda, state and declare as follows:
- 1. I am Director, Patent Department, Sankyo Company Limited (Sankyo), of Tokyo Japan.
- 2. I make this declaration in support of the application for extension of the above-identified US patent 4,486,425, being submitted concurrently herewith pursuant to 35 USC 156 and 37 CFR 1.740.
 - 3. Sankyo Company Limited is the sole assignee of US patent 4,486,425.
- 4. Due to a misunderstanding between Sankyo and Sankyo's US licensee, The Upjohn Company of Kalamazoo, Michigan, Sankyo was not aware that an extension application had not been filed for this patent until they received a telefax from Upjohn on December 4,1992.
- 5. Sankyo intended to file an extension application for the above identified patent according to the provisions of 35 USC 156 and 37 CFR 1.740 and the failure to file such an application until now was completely unintentional.

12月 78 (月) 18:42 サンキョウ(カフェ) トゥキョフェ 03-492-375

PATENT/Docket No. 4722 EX U.S. Patent 4,486,425 Application for Extension Appendix F-2

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and believe are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are purishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

SANKYO COMPANY, LIMITED

December 7, 1992

Date

Signature

Hiroshi Oda

Director Patent Department